DEEP VEIN THROMBOSIS IN A MEDICAL WARD – INCIDENCE AND RISK FACTORS

A dissertation submitted in partial fulfillment of the rules and regulations for the MD Branch – I General Medicine Degree Examination of the Tamil Nadu Dr. M.G.R. Medical University, Chennai, held in April 2016.

DECLARATION CERTIFICATE

This is to declare that the dissertation titled "Deep vein thrombosis in a medical ward – Incidence and Risk factors" is my own work, done under the guidance of Dr. J.V. Peter, Professor, Medical ICU and Dr. Thambu David, Professor and Head, Department of Medicine 2, submitted in partial fulfillment of the rules and regulations for the MD Branch I – General Medicine Degree Examination of the Tamil Nadu Dr. M.G.R. Medical University, Chennai, to be held in April 2016

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Certificate

This is to certify that the dissertation "**Deep vein thrombosis in a Medical ward – Incidence and Risk Factors**" is a Bonafide work of Dr Audrin Lenin carried out under our guidance towards the M.D. Branch I (General Medicine) Examination of the Tamil Nadu Dr M.G.R. University, Chennai to be held in 2016

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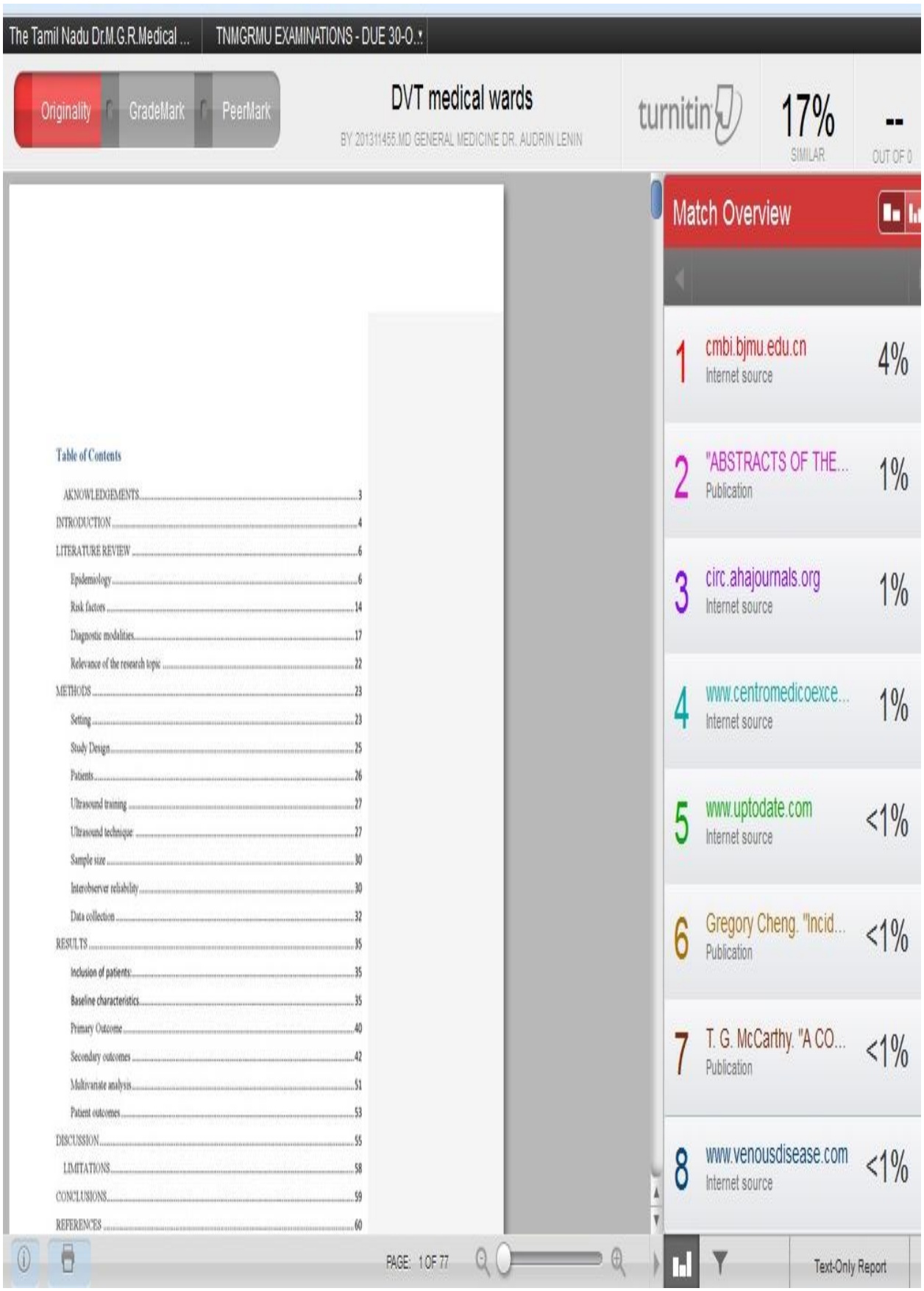
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Incidence and risk factors of deep venous thrombosis among patients admitted to a medical ward at a tertiary hospital in South India.
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Ref: IRB Min No: 8832 [OBSERVE] dated 07.04.2014

Dear Dr. Audrin Lenin,

I enclose the following documents:-

1. Institutional Review Board approval 2. Agreement

Could you please sign the agreement and send it to Dr. Nihal Thomas, Addl. Vice Principal (Research), so that the grant money can be released.

With best wishes,

Dr. Nihal Thomas
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Dear Dr. Audrin Lenin,

The Institutional Review Board (Blue, Research and Ethics Committee) of the Christian Medical College, Vellore, reviewed and discussed your project entitled "Incidence and risk factors of deep venous thrombosis among patients admitted to a medical ward at a tertiary hospital in South India." on February 19, 2014.

The Committees reviewed the following documents:

1. IRB Application format
2. Curriculum Vitae' of Drs. Audrin Lenin, John Victor Peter, Thambu David, Sudha Jasmine, Ravikar Ralph, Nathaniel Samson Devakiruba.
3. Informed Consent form (English, Tamil, Telugu, Hindi & Bengali)
4. Consent form (English, Tamil, Telugu, Hindi & Bengali)
5. No of documents 1-4

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The following Institutional Review Board (Blue, Research & Ethics Committee) members were present at the meeting held on February 19, 2014 in the CREST/SACN Conference Room, Christian Medical College, Bagayam, Vellore 632002.

Name	Qualification	Designation	Other Affiliations
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Dr. Inian Samarasam	MS, FRCS, FRACS	Professor, Surgery, CMC	Internal, Clinician
Dr. Anup Ramachandran	Ph. D	The Wellcome Trust Research Laboratory Gastrointestinal Sciences, CMC, Vellore	Internal, Basic Medical Scientist
Dr. Jacob John	MBBS, MD	Associate Professor, Community Health, CMC, Vellore	Internal, Clinician
Dr. Niranjan Thomas	DCH, MD, DNB (Paediatrics)	Professor, Neonatology, CMC, Vellore	Internal, Clinician
Dr. Vivek Mathew	MD (Gen. Med.) D.M (Neuro) Dip. NB (Neuro)	Professor, Neurology, CMC, Vellore	Internal, Clinician
Dr. Anand Zachariah	MBBS, PhD	Professor, Medicine, CMC, Vellore	Internal, Clinician
Dr. Chandra Singh	MS, MCH, DMB	Professor, Urology, CMC, Vellore	Internal, Clinician
Mrs. Pattabiraman	B. Sc, DSSA	Social Worker, Vellore	External, Lay person
Mr. C. Sampath	B. Sc, BL	Legal Expert, Vellore	External, Legal Expert

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We approve the project to be conducted as presented.

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The Institutional Ethics Committee expects to be informed about the progress of the project, any **adverse events** occurring in the course of the project, any **amendments in the protocol and the patient information / informed consent**. On completion of the study you are expected to submit a copy of the **final report**. Respective forms can be downloaded from the following link: http://172.16.11.136/Research/IRB_Polices.html in the CMC Intranet and in the CMC website link address: http://www.cmch-vellore.edu/static/research/Index.html.

Fluid Grant Allocation:

A sum of Rs. 1,00,000/- (Rupees One Lakh Only) will be granted for 2 years. 50,000/- INR (Rupees Fifty Thousand only) will be granted for 12 months as an Ist Installment. The rest of the 50,000/- INR (Rupees Fifty Thousand only) each will be released at the end of the first year as 2 nd Installment following the receipt of the Interim progress/Annual report and subsequent submission of it to the IRB.

Yours sincerely

Dr. Nihal Thomas
Secretary (Ethics Committee)
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I would like to thank Dr. Pavithra Mannam, Assistant Professir, Department of Radiology, for helping me learn to use a ultrasound probe inspite of having abusy schedule and helping me with the reliability exercise (validation study).

My heartfelt thanks goes to Mrs. Tunny Sebastian, Department of Biostatistics, for her involvement in the analysis of our study results.

INTRODUCTION

A “Thrombus” is defined as a blood clot lodged in the blood vessel. When the pathologic processes overwhelm the regulatory mechanisms of hemostasis, there is excessive formation of thrombin, initiating thrombosis. (1) The thrombus can cause vascular occlusion

Deep venous thrombosis is blood clot in the larger veins. They usually involve the veins of the lower limb. Ocasionally, the clot from the lower limb can dislodge and travel along the venous system, the heart and get occluded in the pulmonary vasculature. This is called pulmonary embolism.

Venous thromboembolism is a term that includes both, deep venous thrombosis and pulmonary embolism, which in itself, is a sequele of the former.(2)

Deep venous thrombosis is defined as formation of a blood clot in the deep venous system. A deep venous thrombosis can occur either in the upper limbs or the lower limbs. In the lower limbs, the deep venous thrombosis is classified as either proximal, involving the femoral vein and distal involving the popliteal veins. The proximal lower limb deep venous thrombosis is usually associated with serious chronic diseases such as malignancies, biventricular failure and acute respiratory distress; whereas, distal lower

limb deep venous thrombosis is associated with transient risk factors such as recent surgery, immobilization and travel.

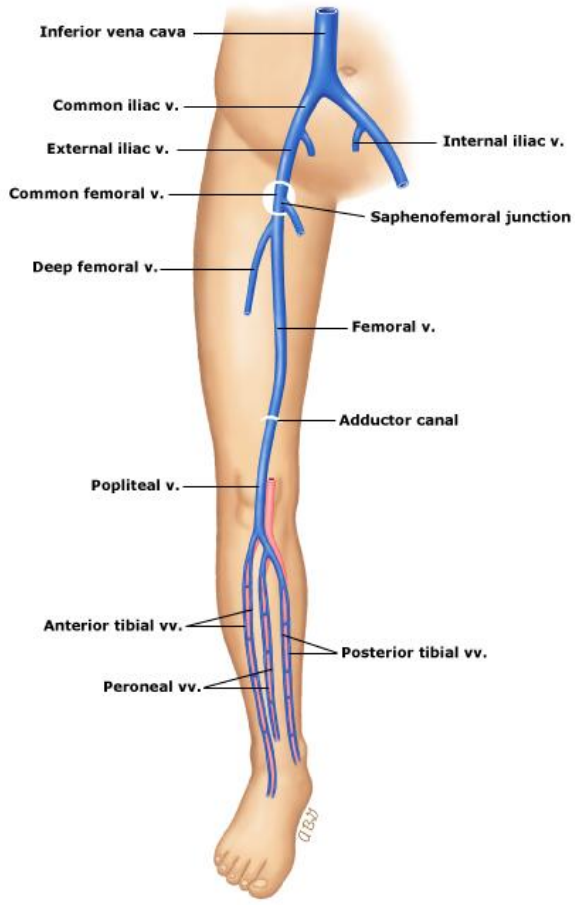


Figure 1 Deep venous system of the lower limb

AIMS AND OBJECTIVES

The aim of the study was to To assess the incidence of deep venous thrombosis and the risk factors favouring its development in patients admitted to a medical ward.

Primary Objective:

The incidence of Deep Vein Thrombosis in patients admitted to a medical ward.

This study was done in patients getting admitted in C ward under The Department of Medicine, Unit 2.

Secondary Objectives:

To assess the risk factors for development of deep vein thrombosis in patients admitted in a medical ward.

To assess the patient outcomes among patients who are admitted with deep vein thrombosis admitted in a medical ward.

LITERATURE REVIEW

Epidemiology

Global scenario

The annual incidence of DVT is estimated at 1-3 per 1000 adult population.(3) A community wide survey done in Worcester showed an annual incidence of 48 people in 100000 population of developing deep venous thrombosis (4). In other studies, the incidence of first-time symptomatic VTE directly standardized for age and sex to the United States population ranged from 71 to 117 cases per 100,000 population (5).

In one study estimating the proportion of hospitalized patients at risk for deep venous thrombosis DVT prophylaxis, it was shown that 36-73% of hospitalized patients all over the world, were at risk of developing deep venous thrombosis. Among the hospitalized medically ill patients, 21-71% of patients were at a high risk of developing deep venous thrombosis. (6)

Venous thromboembolism is associated with significant contribution to health care cost. In 2010, the estimated heath care cost because of hospital acquired venous thromboembolism in the United States ranged from 6.8 to 36 billion dollars (7).

According to the Seventh ACCP Conference on Antithrombotic and Thrombolytic therapy (8), the absolute risk of development of DVT in hospitalized medical patients was 10-20%. Hospitalization for an acute medical illness was independently associated with about an eight-fold increased relative risk for venous thromboembolism. It accounted for almost a quarter of all venous thromboembolism in the general population.

Table 1 **Absolute risk of DVT in Hospitalized patients**

Table 4—*Absolute Risk of DVT in Hospitalized Patients

Patient Group	DVT Prevalence, %
Medical patients	10–20
General surgery	15–40
Major gynecologic surgery	15–40
Major urologic surgery	15–40
Neurosurgery	15–40
Stroke	20–50
Hip or knee arthroplasty, hip fracture surgery	40–60
Major trauma	40–80
Spinal cord injury	60–80
Critical care patients	10–80

*Rates based on objective diagnostic testing for DVT in patients not receiving thromboprophylaxis.

The Mednox study (9); an international, randomized, double-masked, placebo control trial; the role of enoxaparin in preventing thrombosis was evaluated. In the study, 1102 acutely ill, immobilized general medical patients enrolled. The diagnosis of DVT was made based on mandatory lower limb contrast venography, compression ultrasound,

clinical suspicion of deep vein thrombosis, pulmonary embolism confirmed by pulmonary angiography or high-probability lung scan, or, fatal pulmonary embolism. The incidence of DVT among the acutely ill medical ward patients was 14.9%. The incidence was 5.5% in patients receiving low molecular weight heparin.

In the Longitudinal investigation of thromboembolism aetiology (LITE) (10), the information from two prospective cohort studies, Artherosclerosis Risk in Communities (ARIC) and Cardiovascular Health Study (CHS) were combined. The incidence of symptomatic deep venous thrombosis and pulmonary embolism in 21,680 patients over the age of 45 years was determined. The patients were followed up for a mean duration of 7.6 years. The age standardized incidence of first-time venous thromboembolism was 1.92 per 1000 person-years. The rates were higher in men than women. The incidence increased with age.

According to White et al, among the population of California, the incidence of venous thromboembolism was 23 per 100,000 among Caucasians; 29 per 100,000 among African Americans; 14 per 100,000 among Hispanics; and 6 per 100,000 among Asian-Pacific Islanders.(11)

Scenario in Asia

Among the Asian population, the incidence of in hospital venous thromboembolism is lower than in the Caucasian population. In a study by Gore et al, the prevalence of venous thromboembolism was compared between autopsy specimens from Boston, USA and

Kyushu, Japan. The prevalence of venous thromboembolism was much higher in North America (15%) compared to Japan (0.7%) (12)

The reason for the lower incidence of venous thromboembolism among Asian population is not known. It may be related to the lower levels of Factor V Leiden in the Asian population (0.5%) compared to American population (5%)

In the Asian population, a study done in Hong Kong on the Incidence of DVT in hospitalized Chinese medical patients (13) reviewed all Doppler ultrasound studies performed for deep vein thrombosis for the period from 1 January 2005 to 31 December 2008. The presence of risk factors, deep venous thrombosis prophylaxis, number of patients who developed deep venous thrombosis during hospitalization and readmission within 14 days for deep venous thrombosis were looked at. According to the study, the incidence of deep venous thrombosis over a period of 4 years was

- 1.8% in 2005
- 2.0% in 2006
- 1.7% in 2007
- 1.1% in 2008

Table 2 Incidence of DVT in Hong Kong

TABLE 1

Year	2005	2006	2007	2008	2008 versus 2005–7
Proximal DVT incidence (cases detected)	1.8% (182)	2.0% (204)	1.7% (173)	1.1% (128)	$P < .001$
Age range	20–99	17–83	18–100	18–98	NS
Male : female ratio	1 : 1.2	1 : 1.36	1 : 1	1 : 1.4	NS

Indian scenario

There is no data available on the incidence and prevalence of DVT in the general population. The annual incidence of DVT in India is estimated to be at one percent of adult population above the age of forty years and 15-20% among hospitalized patients.(14)

In India, a prospective study done among medically ill patients in a tertiary hospital in North India (15) looked at the incidence of deep venous thrombosis among medically ill hospitalized patients. Consecutive adult patients, more than 18 years of age, admitted to the medical wards and ICU at AIIMS New Delhi from July 2006 to July 2008. Venous ultrasounds were performed at admission and once after 12+/-8 days of hospitalization. A total of 163 patients were screened of which 5 patients developed DVT (3%). The incidence rate of DVT calculated was 2.7 per 1000 person-days of hospital stay.

In the study, the patients who developed DVT, the most frequent underlying disease was infectious disease. Two of the patients had pulmonary infection and one had a GIT infection. The other underlying illnesses associated with DVT were haematological

disease and psychiatrical illness. The patients with DVT had a significant higher duration of hospital stay.

Table 3 Primary Medical-illness necessitating hospitalization in the study population

Table I. Primary medical-illness necessitating hospitalization in the study population

Underlying disease*	Patients without DVT (n = 158)	Patients with DVT (n = 5)
Infectious diseases	97 (61)	3 (60)
Pulmonary infection	53 (33)	2 (40)
GI and liver infection	12 (8)	1 (20)
Genitourinary infection	4 (2)	-
CNS infection	8 (5)	-
Systemic infection	20 (13)	-
Malignancy	9 (6)	-
Chronic pulmonary disease	27 (17)	-
Cardiac disease	5 (3)	-
Rheumatic disease	21 (13)	-
Endocrine disease	4 (2)	-
Acute poisoning	3 (2)	1 (20)
Hematological disease	2 (1)	-
Hepatic disease	5 (3)	-
Neurological disease	6 (4)	-
Others	2 (1)	-
Psychiatric illness	-	1 (20)

Data presented as n (%); *, not mutually exclusive, some patients had multiple underlying diseases; DVT, deep venous thrombosis; GI, gastrointestinal; CNS, central nervous system

Table 4 **Demographic profile of patient with DVT in New Delhi**

Table II. Demographic profile and risk factors in patients with and without DVT

Risk factor	Patients without DVT (n = 158)	Patients with DVT (n = 5)
Age, yr [mean ± SD (range)]	44 ± 18 (18-85)	40 ± 13 (25-50)
Male sex	86 (54)	2 (40)
Duration of hospital stay, days [mean ± SD(range)]	21.3 ± 12.2 (1-62)	33.5 ± 33.2 (10-30)
Smoking	54 (34)	2 (40)
Alcoholism	29 (18)	1 (20)
Known hypercoagulable state	0	0
Malignancy	11 (7)	0
Hematological disorder	4 (2)	1 (20)
Surgery	5 (3)	0
Trauma	9 (6)	0
Immobilization	158 (100)	5 (100)
Intake of OCPs	1	0
Past history of DVT	0	0
Varicose veins	1	0
Central venous catheterization	10 (6)	1 (20)
Mechanical ventilation	43 (27)	2 (40)

Data presented as n (%), unless specified; DVT, deep venous thrombosis; OCPs, oral contraceptive pills

In a retrospective study carried out at Christian Medical College, Vellore, India (16); in-patient records from January 1996 to December 2005 were analyzed. Deep venous thrombosis was diagnosed based on duplex ultrasonography and a diagnosis of

pulmonary embolism was made based on a combination of CT Angiogram, CQ scan, D-dimer and ECG. 722 patients were diagnosed to have venous thromboembolism in 438667 admissions, with an incidence of 17.46 per 10000 admissions. The incidence increased over time and stabilized at about 22 per 10000 admissions.

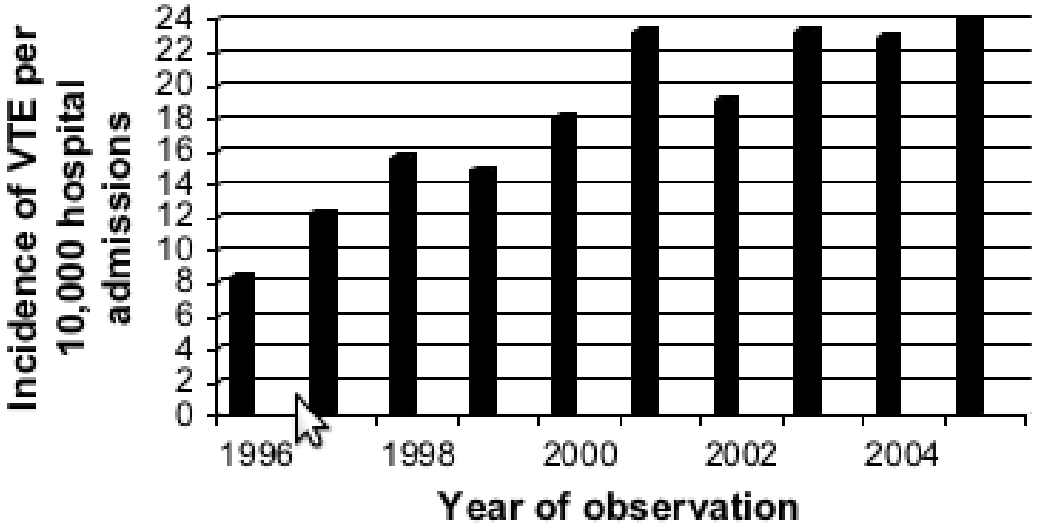


Figure 1 Distribution of VTE over time.

Figure 2 **Distribution of venous thromboembolism over time**

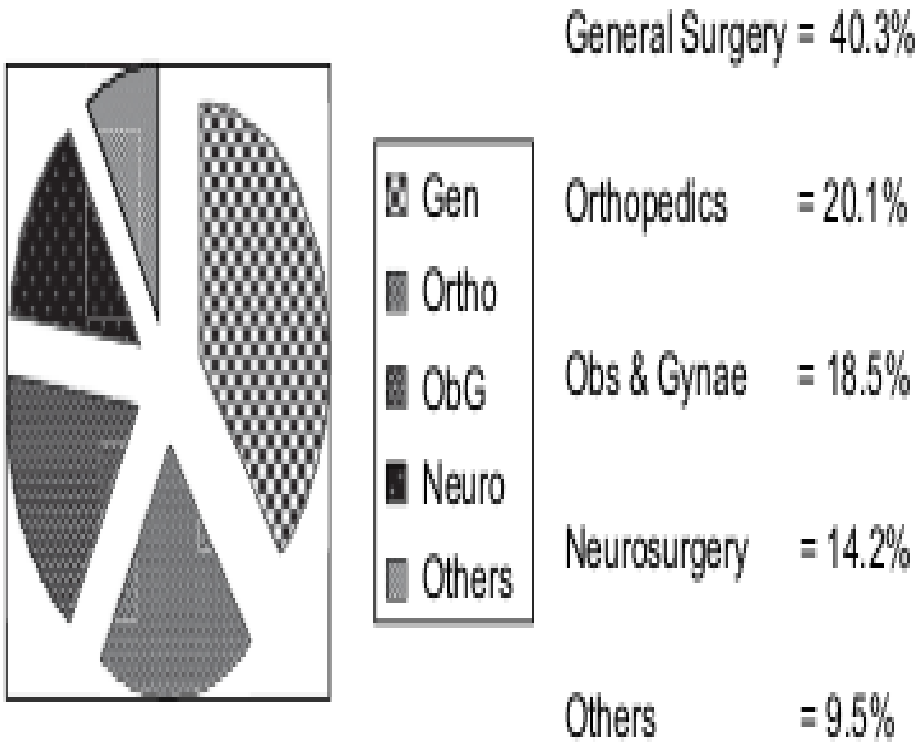


Figure 2 Distribution of DVT according to specialty. General surgery = 40.3%, Orthopaedics = 20.1%, Obstetrics and gynecology = 18.5%, Neurosurgery = 14.2%, Others = 9.5%.

Figure 3 Distribution of venous thromboembolism according to speciality

Risk factors

There are multiple risk factors associated with development of deep venous thrombosis and embolism.

In the MEDNOX study (9), 1102 acutely ill , immobilized general medical patients enrolled in the MEDENOX study, multiple logistic regression analysis found the following factors to be significantly and independently associated with an increased risk for venous thromboembolism.

- Presence of an acute infectious disease
- More than 75 years of age
- History of malignancy
- Prior history of venous thromboembolism

Table 5 Incidence of venous thromboembolism by reason of illness

Table 1. Incidence of Venous Thromboembolism (Days 1-14) by Reason of Illness

Illness	Patients/Events, No.* (%)		
	All (n = 866)	Placebo Group (n = 288)	Enoxaparin Sodium Group (40 mg) (n = 291)
Heart failure			
Yes	34/290 (11.7)	14/96 (14.6)	4/99 (4.0)
No	68/576 (11.8)	29/192 (15.1)	12/192 (6.3)
NYHA class III			
Yes	23/217 (10.6)	9/73 (12.3)	4/78 (5.1)
No	79/649 (12.2)	34/215 (15.8)	12/213 (5.6)
NYHA class IV			
Yes	11/73 (15.1)	5/23 (21.7)	0/21 (0)
No	91/793 (11.5)	38/265 (14.3)	16/270 (5.9)
Acute respiratory disease			
Yes	42/457 (9.2)	20/153 (13.1)	5/153 (3.3)
No	60/409 (14.7)	23/135 (17.1)	11/138 (8.0)
Acute infectious disease			
Yes	64/463 (13.8)	24/155 (15.5)	10/159 (6.3)
No	38/403 (9.4)	19/133 (14.3)	6/132 (4.5)
Acute infectious and respiratory disease			
Yes	27/239 (11.3)	13/79 (16.5)	4/88 (4.6)
No	75/627 (12.0)	30/209 (14.3)	12/203 (5.9)
Acute rheumatic disease			
Yes	14/78 (17.9)	6/29 (20.7)	2/20 (10.0)
No	88/788 (11.2)	37/259 (14.3)	14/271 (5.2)
Inflammatory bowel disease			
Yes	0/5 (0)	0/1 (0)	0/3 (0)
No	102/861 (11.8)	43/287 (15.0)	16/288 (5.6)

Abbreviation: NYHA, New York Heart Association.
*Number of patients in subgroup/number of venous thromboembolic events.

Table 6 Potential risk factors for venous thromboembolism

Table 3. Univariate Logistic Analysis of Potential Risk Factors for Definite Venous Thromboembolism (VTE) in the MEDENOX[5] Study Population

Risk Factor	Relative Risk (95% Confidence Interval)	χ^2	*P* Value
Sex	1.20 (0.83-1.73)	0.76	.38
Age >75 y	1.51 (1.03-2.20)	4.22	.04
Cancer	1.74 (1.13-2.68)	5.46	.02
Previous VTE	1.84 (1.15-2.94)	5.29	.02
Obesity	1.04 (0.68-1.60)	0.03	.97
Varicose veins	1.34 (0.91-1.97)	1.83	.18
Hormone therapy	0.49 (0.07-3.34)	0.15	.71
Chronic respiratory disease	0.60 (0.42-0.88)	6.64	.01
Chronic heart failure	0.72 (0.47-1.11)	1.98	.16

Table 7 Relationship between acute medical illness and venous thromboembolism

Table 4. Univariate Logistic Analysis of the Relationship Between Acute Medical Illness and Risk of Venous Thromboembolism in All 866 Patients

Acute Medical Illness	Relative Risk (95% Confidence Interval)	χ^2	*P* Value
Heart failure	0.99 (0.67-1.46)	0.01	.94
NYHA class III	0.87 (0.56-1.35)	0.25	.62
NYHA class IV	1.31 (0.74-2.34)	0.52	.47
Acute respiratory disease	0.63 (0.43-0.91)	5.72	.02
Acute infectious disease	1.47 (1.47-2.14)	3.59	.05
Acute rheumatic disease	1.61 (0.96-2.69)	2.52	.11
Inflammatory bowel disease*	...	...	...

Abbreviation: NYHA, New York Heart Association.
*Could not be analyzed because there were no events in patients with this disease.

According to the LITE study (10), the conditions associated with venous thromboembolism were hospitalization (52%), malignancy (48%), surgery (42%) and major trauma (6%).

Risk factors for hospitalized DVT

According to the Seventh ACCP Conference on Antithrombotic and Thrombolytic therapy (8), the major risk factors for development of venous thromboembolism in patients hospitalized with acute medical illness were

- NYHA class III and IV heart failure
- COPD exacerbations
- Sepsis

- Advanced age
- Cancer
- Stroke with lower extremity weakness
- Bed rest

In a retrospective observational study done in CMC Vellore (16), referred to earlier, 722 patients with venous thromboembolism was diagnosed in 438667 admissions, the most commonly noted risk factors were malignancy (31%), postoperative (30%), other medical conditions (21%), haematological conditions (12%) and trauma (4%).

Diagnostic modalities

Contrast Venography

Contrast venography has long been considered the gold standard for diagnosis of deep venous thrombosis. In contrast venogram, an intravenous contrast agent is injected in the veins and serial radiographs or fluoroscopy is done is to view the contrast flow. It is an invasive investigative modality The validity of using contrast venography for the diagnosis of deep venous thrombosis was established in a study (17) that evaluated the course of 160 patients suspected clinically of having DVT in whom contrast venography was negative. During a six-month follow-up, only 1.3 percent developed DVT (95% CI 0.4-5.4 percent).

Contrast venogram is not recommended as an initial screening tool in view of patient discomfort and difficulty in obtaining an adequate study. In a report comparing impedance plethysmography and ultrasound to venography in 127 hospitalized patients with clinically suspected DVT of the lower extremity, venography could not be performed in 20 percent of the cases because of contraindications or technical factors (18). Hence, contrast venography is not an ideal modality for screening of deep venous thrombosis.

Impedence Plethymography

Impedance plethysmography is another investigative modality used for diagnosis of deep venous thrombosis. Impedence plethysmography requires the patient to lie still while a thigh cuff is inflated. The change in the volume of the blood at the calf is measured by the impendence at the calf, determined by electrodes connected around it. Rapid deflation of the cuff and the proportional change of impedance over the subsequent three seconds is measured. This is used to measure the venous outflow obstruction. Impedance plethysmography has a sensitivity of 91% and specificity of 96% for the diagnosis of proximal deep venous thrombosis (19). However, impedance plethysmography requires special equipment and trained personnel to perform, which are not available in most centers.

Impedance plethysmography is the ideal investigative modality for evaluation of recurrent deep venous thrombosis. The impedance plethysmography normalizes at a predicatable rate following the occurrence of the first deep venous thrombosis. A repeat impedance plethysmography became normal in 67% by 3 months and 92% by 9 months, in a series of 161 patients with proven deep venous thrombosis and abnormal impedance plethysmography (20). Normalization is less common with compression ultrasound, occurring at a rate of 60-70% at one year (21).

Compression ultrasound

The most commonly used investigative modality for the diagnosis of deep venous thrombosis is a compression ultrasound. The following features are looked at to make a diagnosis of venous thrombosis using compression ultrasound (22,23)

- Abnormal compressibility of the vein
- Abnormal Doppler flow
- The presence of an echogenic band
- Abnormal change in diameter during Valsalva maneuver

Prospective studies have demonstrated that the lack of compressibility of a vein with the ultrasound probe is highly sensitive (>95%) and specific (>95%) for deep venous thrombosis (23,24)

The limitations of a compression ultrasound are:

- It is not able to detect isolated thrombi in the iliac vein or that portion of the femoral vein within the adductor canal.
- The results are limited in patients with deformities or a plaster cast.
- Serial studies need to be performed when the initial test is negative
- Patients with pelvic neoplasms or abscesses may demonstrate isolated noncompressibility of the femoral vein when thrombosis is absent
- Observer dependent study

In the event of the initial test being negative serial tests need to be done. Approximately 2% of the patients with an initial negative screening by ultrasound develop a positive study when retested 7 days later. A single repeat study which is negative at the end of 5-7 days after an initial negative study is predicative of a less than 1% likelihood of venous thromboembolism over months of follow up (25,26)

Doppler sonography is an accurate investigational modality for the diagnosis of deep venous thrombosis. In one study of consecutive outpatients with clinically suspected deep venous thrombosis, compression ultrasonography had a sensitivity of 100% and specificity of 99% (22). In a study of 1290 patients in whom compression ultrasound was negative for deep venous thrombosis at presentation and at the end of one week, the cumulative rate of venous thromboembolic complications was 0.7 percent at six months. This suggested that very few DVTs are missed by compression ultrasonography (27)

Various studies have looked at physician performed bedside ultrasounds on portable devices for diagnosis of deep venous thrombosis. In one study, emergency department physicians were given a 10 minute training session on the use of a portable ultrasonography apparatus on two points – common femoral vein and popliteal vein. A total of 47 physicians performed 199 2-point compression ultrasounds in the emergency department. This was compared with the ultrasonographic reports from the tests performed by the department of Radiology. The sensitivity was 100% and the specificity was 99% (28).

In another multicenter, retrospective review, a comparison between 128 bedside intensivist-performed compression ultrasonographic studies (IP-CUS) with a formal vascular study (FVS) performed by ultrasound technicians and interpreted by radiologists was done. The physicians received formal training at a three day critical care ultrasonography course. Compared with the formal vascular study, it showed a sensitivity of 86% and specificity of 96%. The median time between the physician performed ultrasound and the formal vascular study was 13.8 hours (29).

In a meta-analysis of 16 studies involving 2379 patients, the accuracy of emergency physician-performed ultrasound (EPPU) for diagnosis of DVT compared with either color-flow duplex ultrasound performed by a radiology department or vascular laboratory, or to angiography; showed a sensitivity of 96% and specificity of 97% (30).

Relevance of the research topic

Deep venous thrombosis is a globally significant complication associated with hospitalization. It is largely preventable by screening for risk factors and prophylaxis.
There have been a lot of studies on deep vein thrombosis in a medical ward in a medical ward in the Asian population and showing a lower incidence compared to the Western data. There is a dearth of studies from India on the same.

Very few studies look at both upper and lower limb deep vein thrombosis. In view of the current trend of increasing frequency of central venous catheters and peripherally inserted central venous catheters, there is a higher chance of developing upper limb deep vein thrombosis than anticipated.

In view of the current knowledge and a lack of data from India, it would be relevant to look at the incidence of deep venous thrombosis in the Medical Ward and the risk factors associated with them.

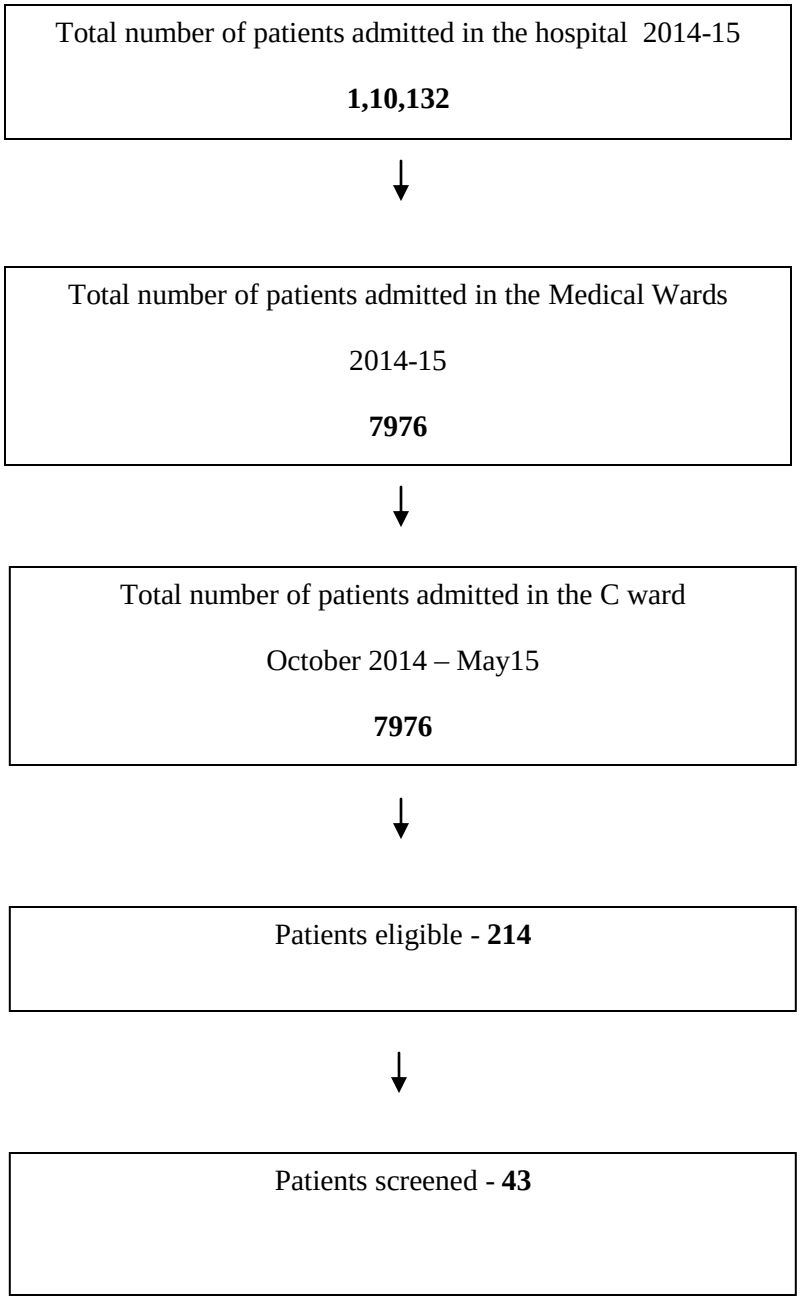
METHODS

Study Setting

This study looked at the incidence of a deep venous thrombosis in a medical ward in a tertiary hospital in South India.

This study was done in Christian Medical College, Vellore, which is a multispeciality, tertiary level hospital located in Vellore, Tamil Nadu. In a year there are 19,00,000 outpatients registrations and 1,20,000 inpatients admissions. In a day; there are 5,500 outpatients seen, 2,500 inpatients and 30 deliveries conducted.

The Department of Medicine has 5 units with a total number of 140 beds in the general ward and a Medical ICU with 12 beds and Medical HDU with 12 beds. The mean duration of hospital stay in the Medical wards is around 6 days.


Total number of patients admitted in the hospital 2014-15
1,10,132
Total number of patients admitted in the Medical Wards
2014-15
7976
Total number of patients admitted in the C ward
October 2014 – May15
7976
Patients eligible - 214
Patients screened - 43

Study Design

The study done was a prospective, observational study with a cohort design. It aimed to look at the incidence and the risk factors for development of a deep venous thrombosis in a Medical Ward.

Primary Objective:

The incidence of Deep Vein Thrombosis in patients admitted to a medical ward.

This study was done in patients getting admitted in C ward under The Department of Medicine, Unit 2.

Secondary Objectives:

To assess the risk factors for development of deep vein thrombosis in patients admitted in a medical ward.

Patients

Inclusion criteria:

We included patients who were

- Age >18 years
- Admitted to the Medical Ward under Medicine unit 2
- Admitted between October 2014 to May 2015

Exclusion criteria:

The following subjects were excluded

- Refusal to give consent
- Patients admitted with a diagnosis of DVT or pulmonary embolism
- Patients on therapeutic anticoagulation

Ultrasound training

The principal investigator was trained in doing Doppler ultrasound for deep venous thrombosis by the Department of Radiology for a period of 1 week. Following the training the validation of the skills of the principal investigator was performed.

Ultrasound technique:

A bedside ultrasound machine (M-turbo Sononsite, dynamic range – 165dB) was used for screening for deep vein thrombosis. The high frequency, vascular probe was used.

Assessment of lower limb DVT:

Patient made to lie supine. A was present while doing the scan on a female patient. The lower limb exposed to visualize the inguinal and the popliteal region.

To assess for the femoral deep vein thrombosis, the patient's leg was externally rotated and flexed to 30 degrees. The probe was placed in the mid-inguinal point. The foot of the probe was held perpendicular to the vessel. The femoral artery was located by with the pulsations. This was confirmed with the colour flow. The vein was located medial to the artery. This was again confirmed with the colour flow and augmentation.

To assess for popliteal deep vein thrombosis, the knee was flexed and the hip externally rotated. The probe was placed in the posteriomedial aspect of the knee, over the popliteal fossa. The foot of the probe was placed perpendicular to the vessel. The popliteal artery was located with the pulsations. This was confirmed with the colour flow. The vein was located superficial to the artery. This was again confirmed with the colour flow and augmentation.

To assess for axillary deep vein thrombosis, the arm was elevated and abducted to expose the axillary region. The probe was placed in the axillary fossa, against the head of humerus. The foot of the probe was placed perpendicular to the vessel. The axillary artery was located with the pulsations. This was confirmed with the colour flow. The vein was located superficial to the artery. This was again confirmed with the colour flow and augmentation. Occasionally, there was an anatomical variation where there are two axillary veins. This was also looked for.

To assess for juglar deep vein thrombosis, the neck was turned to the opposite side. The probe was placed over the anterior border of the sternocleidomastoid, at the level of the crichoid cartilage. The foot of the probe was placed perpendicular to the vessel. The common carotid artery was located with the pulsations. This was confirmed with the colour flow. The vein was located lateral to the artery. This was again confirmed with the colour flow and augmentation.

Diagnosis of a deep venous thrombosis:

In this study, a compression ultrasound was performed to determine the presence of a thrombus. This has shown to have a sensitivity of 100% and specificity of 97% in the hands of emergency physicians. (30). The vein is identified and a gradual pressure is applied downwards with the transducer. Normally, the vein collapses completely with both the walls meeting each other. On removing the pressure, the vein opens again and resumes its original shape. The artery does not collapse so easy and is more resilient.

This compressibility of the vein is indicative of the lack of thrombus in the vein. If the vein does not compress at pressures which cause deformation of the artery, it is diagnostic of a deep vein thrombosis.

Sample size

Assuming an incidence of deep venous thrombosis of 14.9% according to the MEDNOX study (9), with a CI of 05% and error of margin of 5%, the sample size calculated was 196. Assuming an incidence of 15% drop out/loss of data, a sample size of 220 was considered.

The formula used for calculation of the sample size:

Sample size = $[\{Z(1\text{-alpha})\}^2 xPxQ]/ [D^2]$

Z (1-alpha)	-	Confidence interval
P	-	Prevalence
Q	-	[1-P]
D	-	Precision

Statistical analysis

Analysis was done using SPSS version 16 (Copyright 2007). Data was entered in EPIDATA software with quality control checks such as range and consistency. Data quality was further explored using histogram, Box Cox plots and frequency distributions (which was used for continuous variables). Categorical variables have been presented as numbers and percentages and continuous variables as mean and standard deviation (SD).

If the distribution was skewed, besides the mean and SD, Median with interquartile range have also been presented. Categorical variables were analyzed using Chi square test with Yates's correction and Proportion test. Continuous variables were analyzed using Independent sample t test. Non parametric Mann Whitney U test was used when the distribution was skewed. Logistic regression analysis was done to determine the risk factors for DVT with log link. Model assumptions were checked using likelihood residual plots against predicted probability. Goodness of fit of the model was assessed using Hosmer Lemeshow chi-square statistics.

Inter-observer reliability

To assess for the inter-observer reliability and for validation of the skills of the principal observer, a reliability exercise was conducted prior to the initiation of the study. This exercise was done between the principal observer (self) and Dr. Pavithra Mannam, Asst. Professor, Department of Radiology. As the sample size was 196, a total of 40 scans (20% of 196 = 39.2)vwere done by both the Radiologist and the principal observer. Over a period of 8 days, 5 scans were done per day in Medicine 2 ward independently by both. The observers looked for the presence of deep vein thrombosis with a Doppler ultrasound using the compression technique. The data for presence and absence of deep vein thrombosis was calculated between both the observers and Cohen's kappa co-efficient was done.

A kappa value of more than less than 0.4 is a poor inter-observer agreement. A kappa value of 0.4-0.75 is fairly good inter-observer agreement. A kappa value of 0.75 is suggestive of excellent inter-observer agreement.

The data from the 40 scans were analyzed for both the observers. The Kappa value for the overall presence of DVT was 1.0 with a p value of <0.001, suggestive of excellent inter-observer agreement.

Table 8 Kappa's inter-observer variation

Kappa's inter-observer variation		
	Observer 1 (Primary investigator)	Observer 2 (Radiologist)
Positive DVT	1	1
Negative DVT	39	39

Table 9 **Kappa statistics for inter-observer variability**

Kappa statistics for inter-observer variability						
			Observer 2 (Radiologist)			Total
			Positive	Negative		
Observer 1 (Primary investigator)	Positive	Count	1	0		1
		% of Total	2.5%	0.0%		2.5%
	Negative	Count	0	39		39
		% of Total	0.0%	97.5%		97.5%
Total		Count	1	39		40
		% of Total	2.5%	97.5%		100.0%
Symmetric Measures						
		Value		Asymp. Std. Error(a)	Approx. T(b)	Approx. Sig.
Measure of Agreement	Kappa	1.000		<0.0001	6.325	0.000
N of Valid Cases		40				

Data collection

The study protocol was approved by the Institutional review board (*IRB Min. No 8832 [OBSERVE] dated 07/04/2015)*. Ethics committee approval was also obtained. A day 1 clinical research form was filled. This included demographics as well as known risk factors for the development of venous thrombosis. It has been shown that a single repeat study that is negative after 7 days predicts a less than 1% incidence of venous thrombus (26). Hence the Doppler ultrasonography was performed on 1st, 3rd, 7th, 10th, 14th, 21st,

and 30th day of hospital admission for included patients. On day 30 or the day of discharge (whichever was earlier), the clinical research form was completed with regard to the course and complications in the hospital. In the event of the presence of a deep venous thrombosis, the treating team was notified.

The study was done October 2014 to May 2015 in patients admitted in a medical ward under Medicine unit 2 at Christian Medical College, Vellore, a tertiary care center in South India.

The primary outcome looked at was the incidence of development of a deep venous thrombosis in patients admitted in a medical ward using a four point compression ultrasound. A diagnosis of DVT (Deep venous thrombosis) was made if there was non-compressibility using a four point Doppler ultrasound on Day 1, Day 3, Day 7, Day 10, Day 14, Day 21, and Day 30 of hospital admission.

The various exposures looked at were:

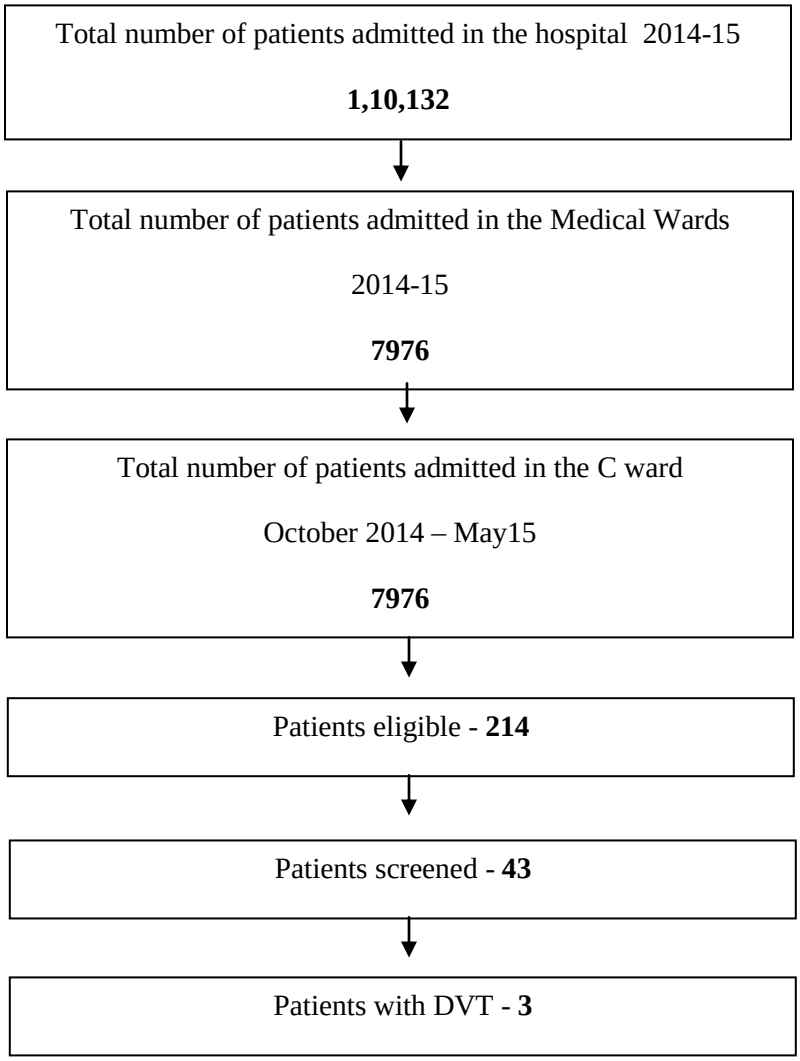
- Age
- Sex
- Previous history of venous thromboembolism
- Whether on any anticoagulation
- Past or present history of malignancy
- Stroke

- History of trauma
- History of surgery
- Central venous catheters
- Dialysis
- Acute respiratory distress
- Congestive cardiac failure
- Hypercoagulable states
- Hormone therapy
- COPD
- Varicose veins
- Mobility status

RESULTS

Inclusion of patients:

There were a total of 1,10,132 admissions in Christian Medical College Vellore in the year 2014-2015. There were a total of 7976 patients who got admitted in Medical wards in the year 2014-2015. During the study period, there were a total of 737 patients who were admitted to the ward. Of these patients 214, were eligible and 43 were screened for the study.



Baseline characteristics

Table 10 **Baseline characteristics – At the time of admission**

Baseline characeteristics – At admission

VARIABLE	FREQUENCY (N=43)
Age in years, Mean (SD)	47 (18.25)
Male, n (%)	22 (51.2)
Malignancy, n (%)	2 (4.7)
Past history of surgery (<3 weeks), n (%)	2 (4.7)
Past history of DVT, n (%)	0 (0)
Past history of Pulmonary embolism, n (%)	0 (0)
Smoking, n (%)	9 (20.9)
Bed bound, n (%)	22 (51.2)
Cerebrovascular accident, n (%)	5 (11.6)
Heart disease, n (%)	6 (14)

The mean age of the patients was 47 years with a standard deviation of 18.25. There was equal male and female predisposition with 51.2% of the population being male.

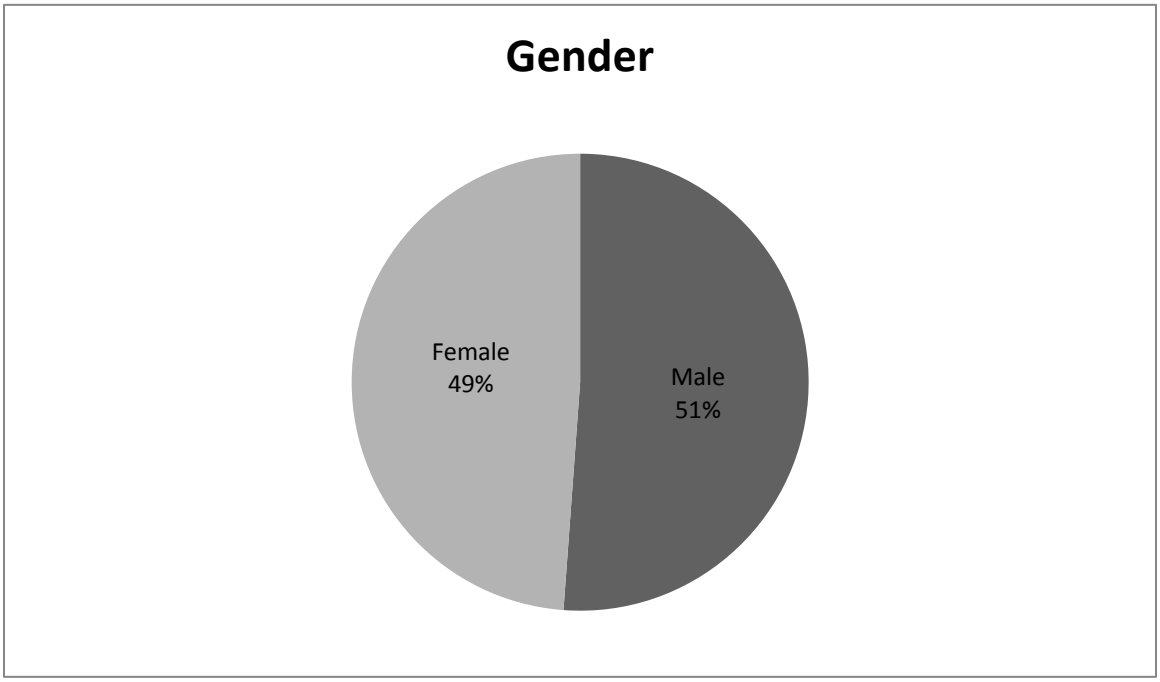


Figure 4 Gender

Out of the 43 patients being studied, 2 (4%) had history of malignancy, 2 (4.7%) had history of surgery in the preceding 3 weeks. The history of smoking was present in 9 (20.9%) of the patients. There were 22 (51.2%) of the patients who were bedbound and dependent on their caretakers for the activities of daily living. There were 5 (11.6%) patients who had cerebrovascular accident and 6 (14%) of patients who had history of heart disease.

Table 11 **Baseline characteristics – In hospital**

Baseline characteristics - in hospital

VARIABLE	FREQUENCY (N-43)
Central venous catheter, n (%)	3 (7)
Dialysis, n (%)	0 (0)
ARDS, n (%)	2 (4.7)
Well's score, Median (range)	1.5 (6)
DVT Prophylaxis, n (%)	12 (27.9)
Duration of hospital stay, median (range)	6 (37)

Of the patients studied 3 (7%) of the patients had central venous catheter insertion. None of the patients had past history of DVT or Pulmonary embolism. None of the patients had dialysis. The median duration of hospital stay was 6 days with a range of 37.

There were 12 patients on DVT prophylaxis constituting 27.9% of the population. Among the 12 patients, 1 (8.3%) were on TED stockings and 11 (91.7%) were on Heparin prophylaxis. The median Well's score was 1.5 with a range of 6.

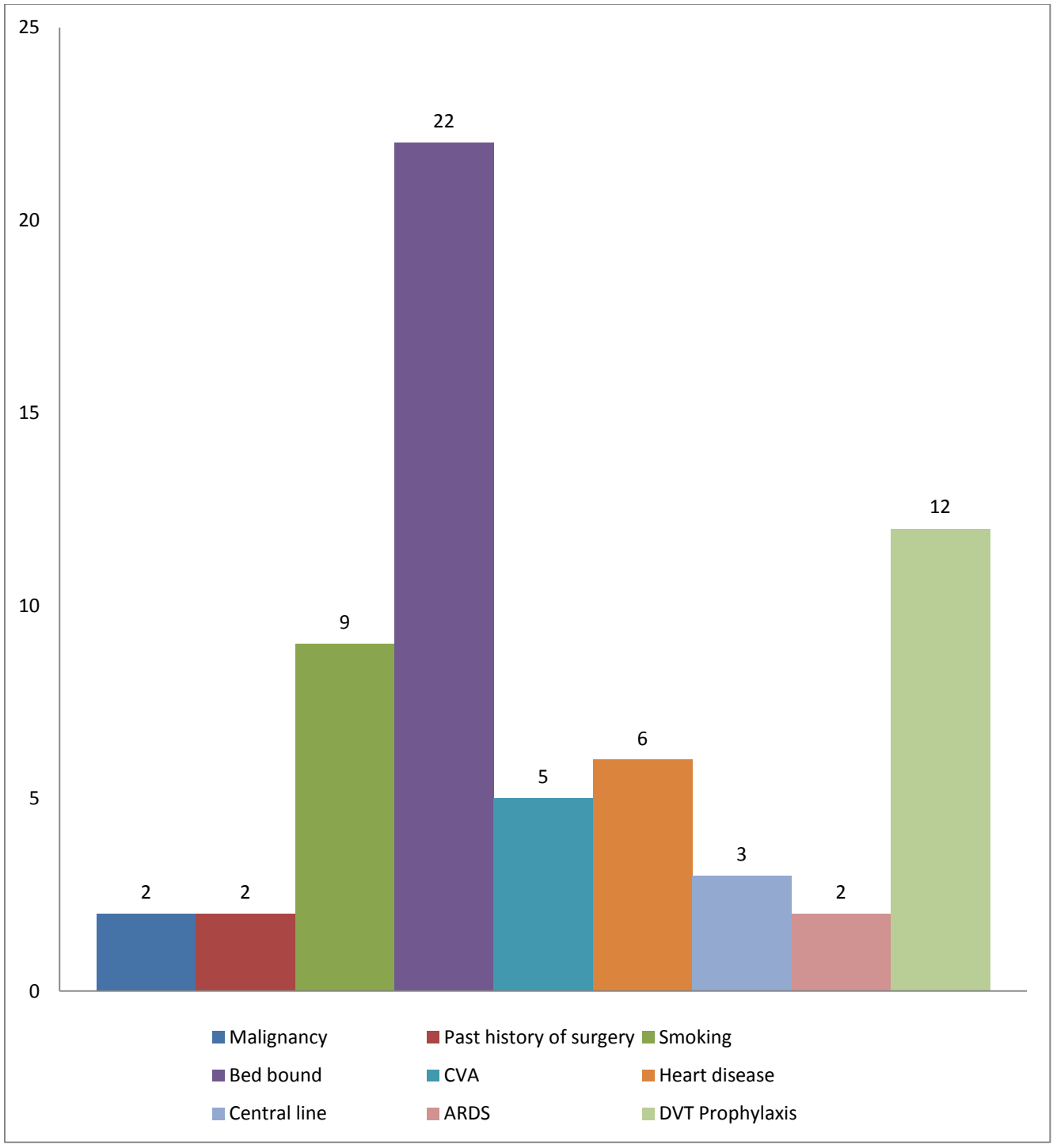


Figure 5 **Baseline characteristics**

Primary Outcome

Among the 43 patients screened for deep vein thrombosis in a Medical ward from October 2014 to May 2015, there were 3 patients who developed deep vein thrombosis (6.98%). The incidence of deep vein thrombosis among the patients admitted in a Medical ward was 7.48 per 1000 patient days.

Table 12 **Primary outcome**

Primary outcome	
Total number of patients screened	43
Total number of positive DVT	3
Percentage of patients who developed DVT	6.98%
Cumulative duration of hospital stay	401 days
Incidence of DVT	7.48 per 1000 patient days

Of the patients who developed deep vein thrombosis, 2 (66.6%) had a deep vein thrombosis in the femoral vein and 1 (33.3%) in the axillary vein.

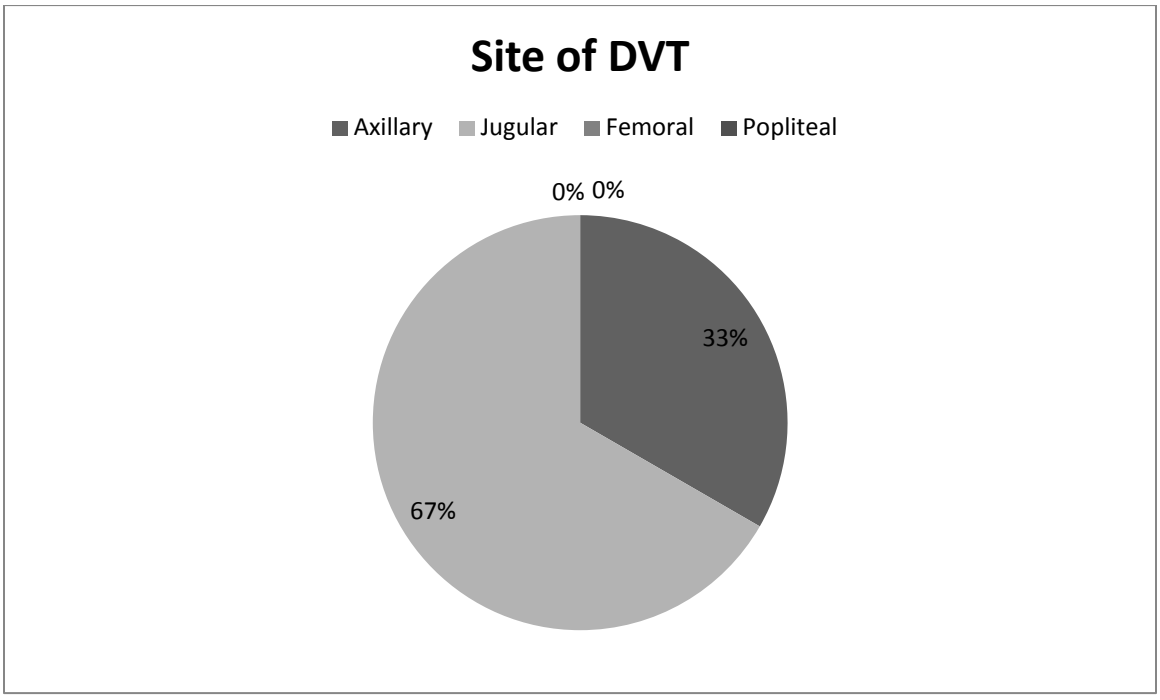


Figure 6 Site of DVT

The patient with the axillary vein thrombosis, developed the deep vein thrombosis secondary to a central venous catheter. She was diagnosed to have cryptococcal meningitis and refractory shock. The central venous catheter was inserted for intravenous antifungal therapy and for shock. She succumbed to her illness.

The two patients with femoral vein thrombosis did not have any central venous catheter done. The treating team was informed about the presence of the deep vein thrombosis and further appropriate therapy was initiated.

Secondary outcomes

The secondary outcome of the study was to look at the risk factors to development of deep vein thrombosis in the patients admitted in a medical ward. A univariate analysis was done among patients screened.

Table 13 **Univariate analysis – part 1**

Univariate analysis – Part 1

VARIABLE	DVT present (N-3)	DVT absent (N-40)	P value
Age >50 years, n (%)	2 (9.5)	19 (90.3)	0.607
Male, n (%)	2 (66)	20	0.578
Malignancy, n (%)	0	2	0.692
Surgery (<3weeks) n (%)	1	1	0.014
Past history of DVT, n (%)	0	0	
Past history of PE, n (%)	0	0	
Smoking, n (%)	1	8	0.584
Bed bound n (%)	2	20	0.578
Cerebrovascular accident, n (%)	0	5	0.515

Table 14 Univariate analysis – part 2

Univariate analysis – Part 2

VARIABLE	DVT present (N-3)	DVT absent (N-40)	P value
Heart disease, n (%)	0	6	0.470
Central venous catheter, n (%)	1	2	0.063
Thrombophlebitis, n (%)	0	1	0.782
Hypercoagulable state, n (%)	0	3	0.623
Dialysis, n (%)	0	0	
ARDS, n (%)	0	2	0.692
DVT Prophylaxis, n (%)	2	10	0.121
Well's score Median (range)	6 (1.5)	1.5 (6)	0.008
Hospital stay >7days, n (%)	3 (16.7)	15 (83.3)	0.066

Age

The mean age of the patients in this study was 47 years. A univariate analysis was done with age more than 50 years and patients with age less than 50 years. Among patients more than 50 years of age, 2 (9.5%) developed DVT and 19 (90.3%) did not develop DVT. The Odds ratio was 2.2 (C.I: 0.2-26.4). The p-value was 0.607. Age was not a significant risk factor for development of in-hospital deep venous thrombosis.

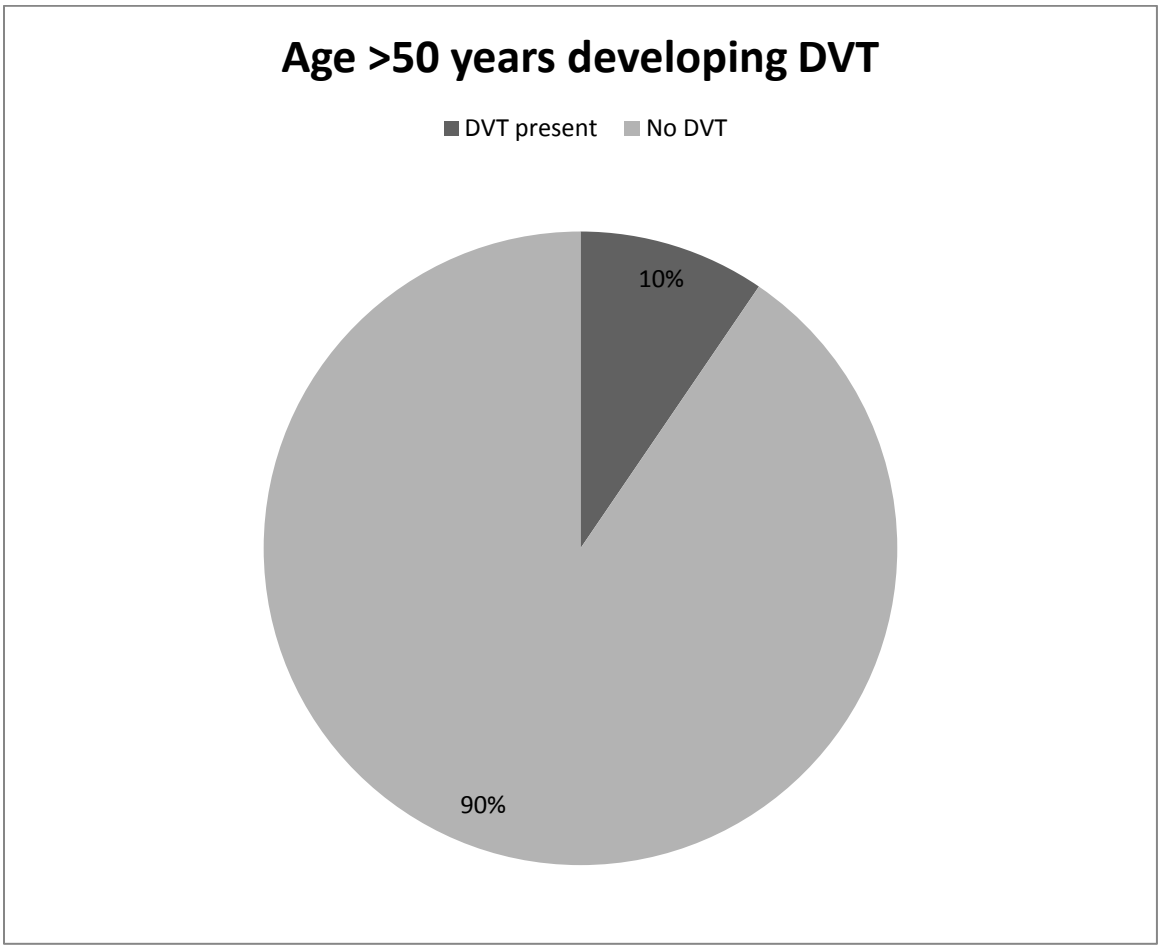


Figure 7 Age >50 years developing DVT

Gender

There were 22 males (51.2%) and 21 females (49.8%) evaluated in this study. A univariate analysis was done among males and females. Among the males 2 (9%) developed deep vein thrombosis and 20 (91%) did not develop deep vein thrombosis. The odds ratio was 2 (C.I: 0.2-23.9). The p-value was 0.578. Age was not a risk factor for development of deep vein thrombosis.

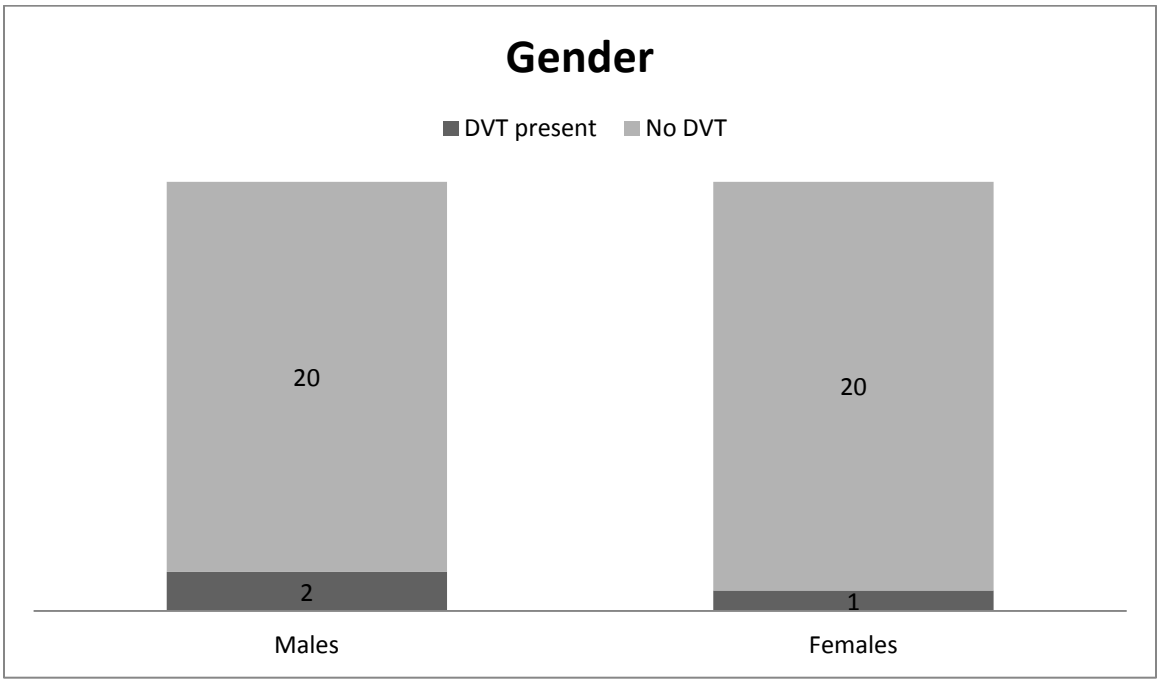


Figure 8 **Gender**

Malignancy

In this study, 2 patients had malignancy, but none of them developed deep vein thrombosis.

Surgery in the past 3 weeks

There were 2 patients who had history of surgery in the preceding 3 weeks prior to admission. 1 patient developed DVT and 1 patient did not develop DVT. The Odds ratio was 19.5 (C.I: 0.87 – 439.3). The p-value was 0.014. Surgery in the preceding three weeks was a risk factor for development of deep vein thrombosis.

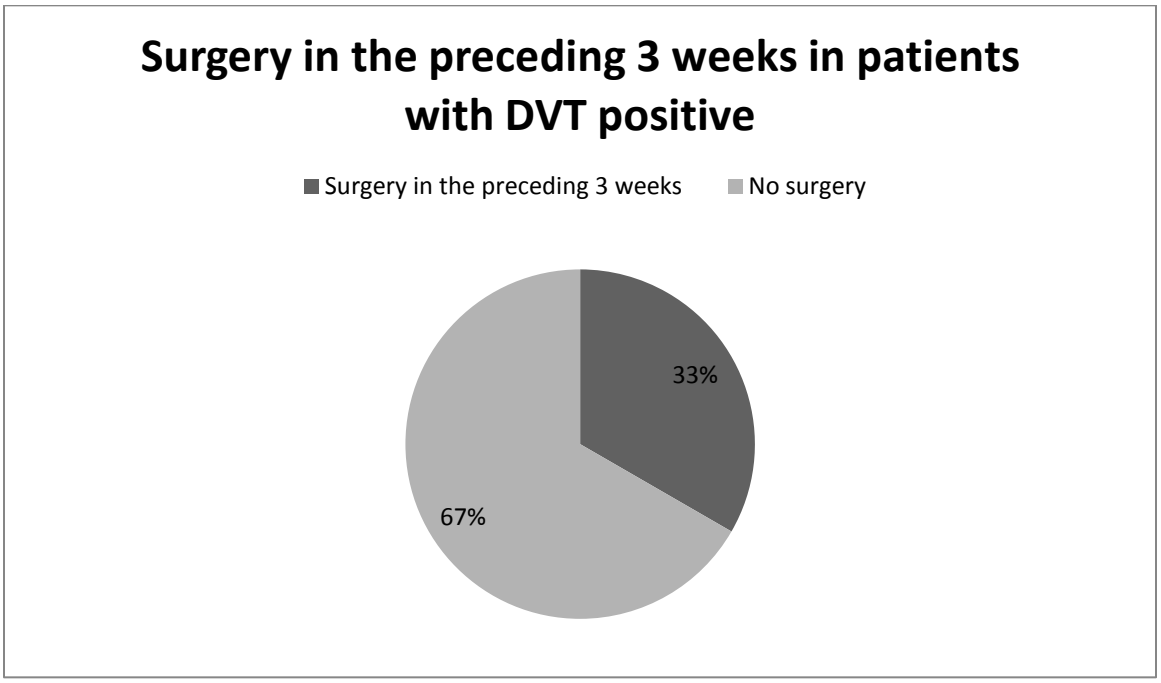


Figure 9 Surgery in the preceding 3 weeks

Smoking

There were 9 patients who had history of beedi/cigarette smoking. Among the 9 patients, 1 (11.1%) developed deep vein thrombosis and 8 (88.9%) did not develop DVT. The

Odds ratio was 2 (C.I: 0.16-24.9). The p-value was 0.584. Smoking was not found to be a risk factor for development of deep vein thrombosis.

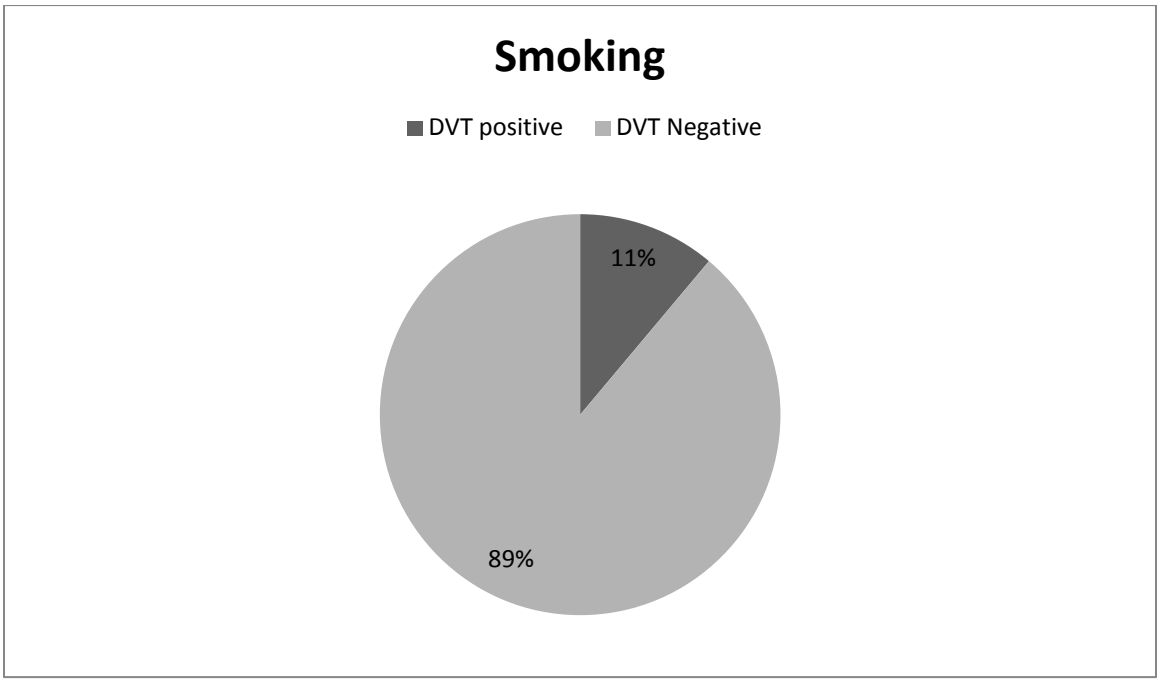


Figure 10 Smoking

Bed bound

Among the patients screened, 22 patients were bed bound. Of the bed bound patients, 2 (9%) developed deep vein thrombosis and 20 (90.9%) did not develop dep vein thrombosis. The Odds ratio was 2 (C.I: 0.17-23.9). The p-value was 0.578. Being bed bound was not found to be a risk factor for development of deep vein thrombosis.

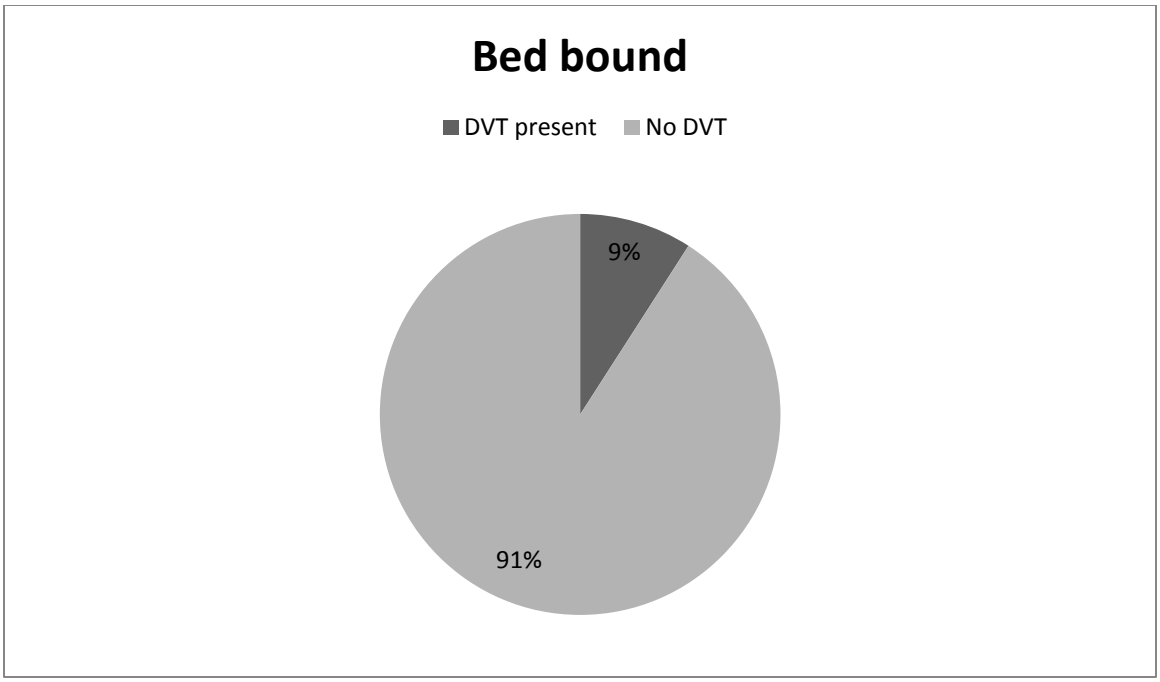


Figure 11 **Bed bound state**

Cerebrovascular accident

In this study, 5 patients had cerebrovascular accident, but none of them developed deep vein thrombosis.

Heart disease

In this study, 6 patients had had history of heart disease, but none of them developed deep vein thrombosis.

Hypercoagulable state

In this study, 3 patients had hypercoagulable state. One patient had polycythemia, one patient had pregnancy and another patient had a haematological malignancy. None of the patients with hypercoagulable state developed deep vein thrombosis.

Acute respiratory distress syndrome

In this study, 2 patients had acute respiratory distress syndrome. None of the patients with acute respiratory distress syndrome developed deep vein thrombosis.

Central venous catheter

In this study, 3 patients had central venous catheters. Among the patients with central venous catheter, 1 (33.3%) developed deep vein thrombosis and 2 (66.7%), did not develop deep vein thrombosis. The Odds ratio was 9.5 (C.I: 0.58-154.7). The p-value was 0.063. Central venous catheter was a risk factor for development of deep vein thrombosis.

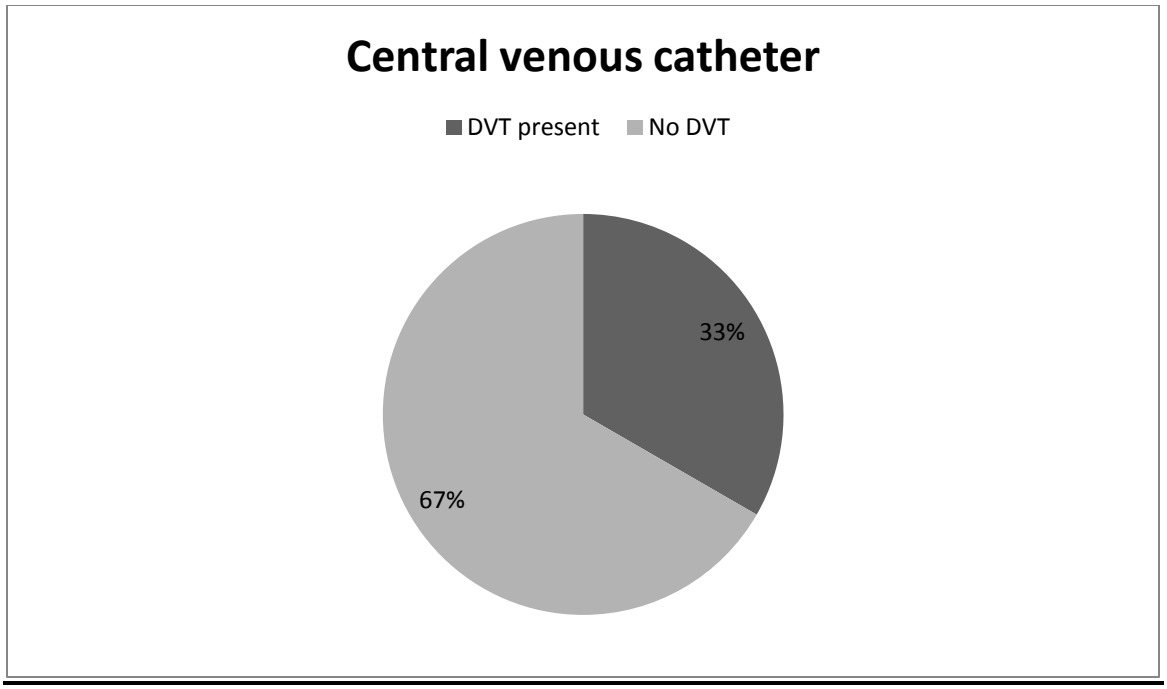


Figure 12 Central venous catheter

Hospital stay

The median duration of hospital stay was 6 days. The patients were divided into hospital stay more than 7 days and less than 7 days. Among patients who had a hospital stay of more than 7 days, 3 (16.7%) had deep vein thrombosis and 15 (83.3%) did not have deep vein thrombosis. The relative risk was 1.2 (C.I: 0.98-1.5). The p-value was 0.066. The development of deep vein thrombosis was associated with a higher duration of hospital stay.

Well's score

The median Well's score in the patients who had deep vein thrombosis was 6 with a range of 1.5. The median Well's score in the patients without deep vein thrombosis was 1.5 with a range of 6. The p-value was 0.008 which was statistically significant.

Multivariate analysis

Among the univariate analysis, the factors which were significant for development of deep vein thrombosis in patients admitted to a medical ward were

1) Surgery in the preceding 3 weeks
2) Central venous catheter
3) Duration of hospital stay
4) Well's score

Multivariate analysis and logistical regression was applied for assessment of independent risk factors.

Table 15 **Multivariate analysis**

Multivariate analysis

Variable	**Odds ratio**	**95% C.I.**	**p-value**
Surgery <3 weeks	2.4	0.38-488	0.120
Central venous catheter	0.4	0.049-433	0.509
Well's score	0.290	0.047-1.772	0.180
Duration of hospital stay	4.7	1.02-1.3	0.029

In the multivariate analysis, surgery in the preceding 3 weeks and central venous catheter insertion were not statistically significant as an independent risk factor for development of deep vein thrombosis. The duration of hospital stay was statistically significant suggestive of a longer hospital stay for patients with deep vein thrombosis.

Patient outcomes

Another secondary outcome looked at in this study was the patient outcomes. The variables looked at were mortality and duration of hospital stay.

Death

In the 43 patients studied, 5 patients had in-hospital death and 3 patients were discharged against medical advice. In the 3 patients who developed deep vein thrombosis in hospital, 1(33%) patient had in-hospital death and 2 (66.7%) patients were discharged in a stable condition. In the patients who did not develop deep vein thrombosis 4 (10%) patients had in hospital death, 3 (7.5%) were discharged against medical advice and 33 (82.5%) patients were discharged in a stable condition. The p-value for mortality was 0.445. There was no statistical difference in mortality among patients with DVT and without DVT.

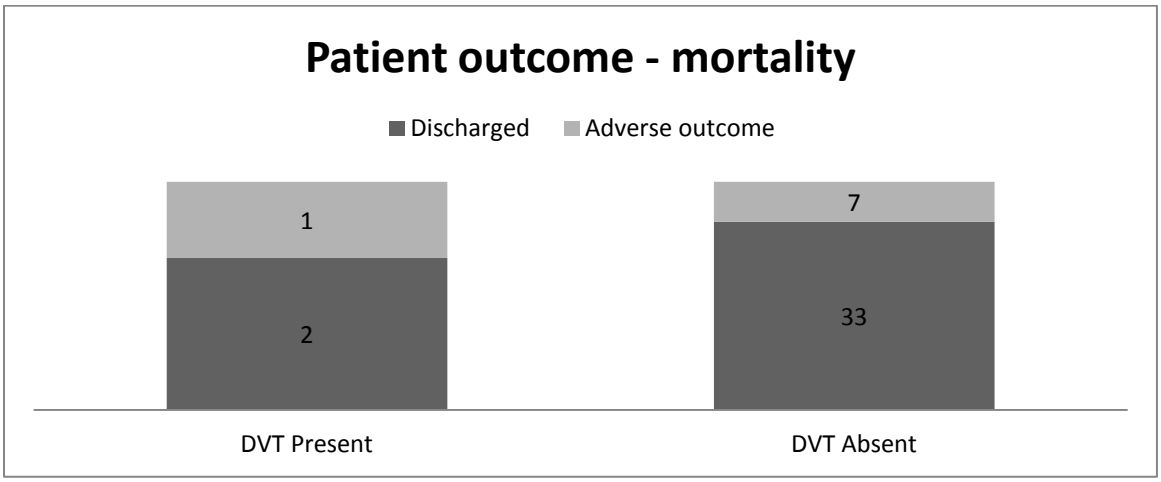


Figure 13 Patient outcomes - mortality

Duration of hospital stay

The mean duration of hospital stay was 9 days. The median duration of hospital stay was 6 days, with a range of 2 – 39 days. The mean duration of hospital stay for patients who developed deep vein thrombosis was 27.33 days. The median duration of hospital stay for patients who developed deep vein thrombosis was 25 days. The mean duration of hospital stay for patients who did not develop deep vein thrombosis was 7.98 days. The median duration of hospital stay for patients who did not develop deep vein thrombosis was 5.5 days.

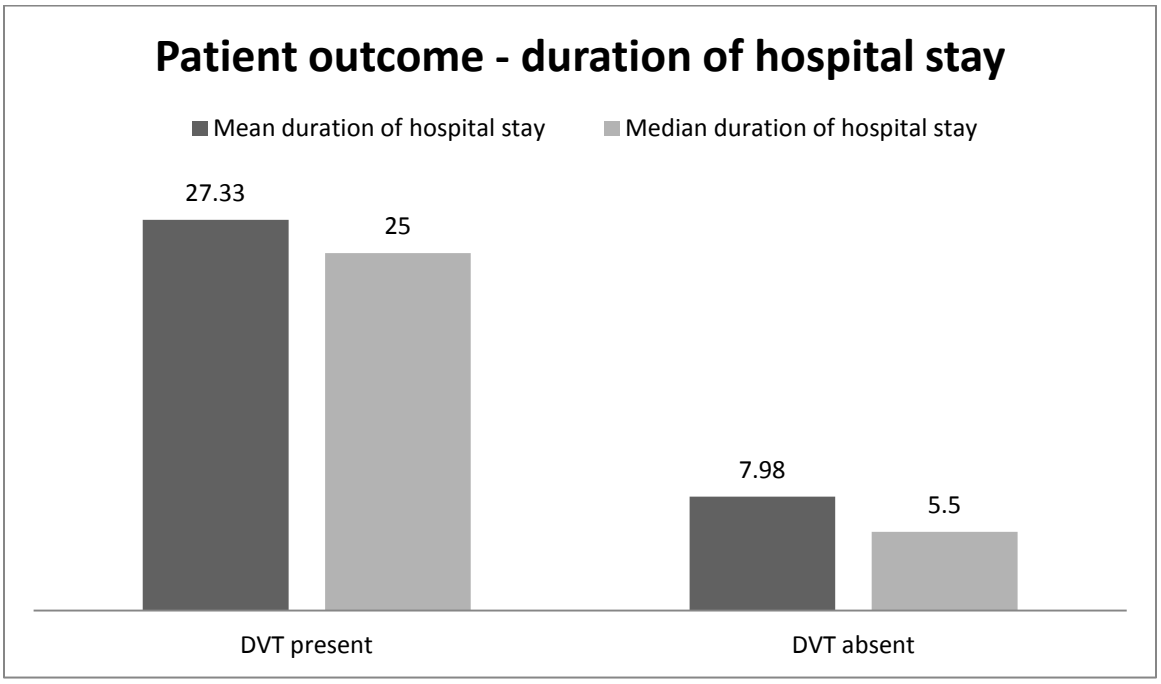


Figure 14 Duration of hospital stay

DISCUSSION

Incidence of DVT in a medical ward

In our medical ward, among the patients screened 6.98 % developed deep vein thrombosis. The incidence of deep vein thrombosis in our medical ward was found to be 7.48 per 1000 patient years. Every 125 days of hospital stay was associated with one deep vein thrombosis event.

Comparison with Indian data

In a study done in patients admitted to ICU and wards AIIMS, New Delhi, 3% of the patients developed DVT with an incidence of 2.7 per 1000 patient-days. The incidence in our study was higher at 7.48 per 1000 patient-days. The higher incidence could be attributed to higher percentage of patients being immobilized and more frequent DVT screening in our study.

Comparison with Asian data

The incidence of deep vein thrombosis in a study done in Hong Kong (13) in a study done among Chinese patients was 1.1%. The incidence in our study was higher than seen in Asian data.

Comparison with global data

The incidence of deep vein thrombosis according to the MEDNOX study (9), was 14.9%. According to the 7th ACCP conference on Antithrombotic and Thrombolytic therapy (8), the absolute risk of development of deep vein thrombosis was 10-20%. The percentage of patients developing deep vein thrombosis in our study (6.98%) was lower than the incidence seen in the West.

Risk factors for deep vein thrombosis

One third of the deep vein thrombosis was secondary to a central venous catheter insertion. The incidence of deep vein thrombosis was higher in males than females, but the difference was not statistically significant. Among patients more than 50 years of age, the incidence of deep vein thrombosis was higher, but the difference was not statistically significant. Patients who had history of surgery in the preceding 3 weeks had a higher risk of developing deep vein thrombosis with an odd's ratio of 19.5.

The incidence of deep vein thrombosis was higher in patients who were smokers, but the result was not statistically significant. Bed bound state was not statistically significant for development of deep vein thrombosis. None of the patients screened with heart disease or cerebrovascular accident developed deep vein thrombosis. This was probably due to DVT

prophylaxis prescribed to patients with cerebrovascular accident and initiation of anticoagulation in patients with heart disease.

None of the patients with hypercoagulable states developed deep vein thrombosis. This was possibly due to initiation of anticoagulation and DVT prophylaxis in patients admitted with known hypercoagulable state.

Among the patients who had central venous catheters inserted during the hospital stay, had a higher incidence of deep vein thrombosis with a odds ratio of 9.5. Out of the 3 patients who developed deep vein thrombosis in this study, 1 patient developed a central line related deep vein thrombosis of the axillary vein. In a study done in 2015 (31), femoral central venous lines had the highest incidence of symptomatic deep vein thrombosis (1.4%) in comparison to subclavian (0.5%) and jugular lines (0.9%). In our study, we had one patient who developed an axillary vein thrombosis (33%)

Patient outcomes

Duration of hospital stay

It was noted in this study that the duration of hospital stay was much higher in patients who developed deep vein thrombosis. Development of deep vein thrombosis was associated with more than four times increase in the duration of hospital stay. The median duration of hospital stay for patients without DVT was 6 days compared to 25 days in patients who developed DVT. A higher duration of hospital stay is associated with higher

risks for the patient including increased exposure to hospital pathogens and infectious agents, complications of anticoagulation and treatment for deep vein thrombosis, higher financial burden and increased duration of follow up after discharge.

Mortality

The mortality rate in patients who developed deep vein thrombosis was 66% compared to 10% in the patients who did not develop deep vein thrombosis. However, this difference was not statistically significant with a p-value of 0.445.

LIMITATIONS

The significant limitation of this study was the number of patients studied. The sample size calculated was 220 and 214 patients were recruited, out of which 43 patients consented for the research. The small number of patients would affect the results of the study.

The study was planned to be done on consecutive patients admitted in the ward, but in view of personal constrains and mechanical issues with the ultrasound machine, was not complete. In this study, as far as possible, consecutive patients were tried to be recruited.

CONCLUSIONS

- The incidence of deep vein thrombosis among patients admitted in a medical ward in a tertiary care hospital in South India was 7.48 per 1000 person-days.

- Hospital admission of more than 7 days was found to be significant independent risk factor for development of deep vein thrombosis in our study

- Deep vein thrombosis prophylaxis should be considered in patients with hospital stay of more than 7 days.

- Further studies need to be done to devise strategies to reduce the development of deep vein thrombosis in these high risk groups.

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ANNEXURE – 1 – Clinical Reseasrch Form

DVT IN MEDICAL WARDS

Clinical Research Form

PART 1

Serial Number :

Name :

Hospital Number :

Age : Gender :

Occupation :

Malignancy	Surgery < 6 weeks	Past DVT
Past PE	Smoking	Bed Bound
CVA	OCPs	Varicose Veins

- **History of heart disease** : Yes No
  - If yes, for how long :
  - Type of heart disease :
  - NYHA class :

PART 2

	DAY 1	**DAY 3**	**DAY 7**	**DAY 10**	**DAY 14**	**DAY 21**	**DAY 30**
LEFT UPPER LIMB							
RIGHT UPPER LIMB							
LEFT LOWER LIMB							
RIGHT LOWER LIMB							

PART 3:

- **Diagnosis** :
- **Central venous catheters inserted** : Yes No
- **Thrombophlebitis** : Yes No
- **Mobility status**
  - Level 1 : (total bed rest or sedentary patient)
  - Level 2 : (level 1 with bathroom privileges)
  - Level 3 : (level 2 with activity as tolerated by the patient)
- **Hypercoagulable state** : Yes No

- **Dialysis** : Yes No
- **ARDS** : Yes No
- **On DVT prophylaxis** : Yes No
  - If yes, prophylaxis modality used :
- **Diagnosed DVT/Pulmonary embolism** : Yes No
- **Duration of hospital stay :**
- **Death**

ANNEXURE 2 - CONSENT FORM

Study title: DVT in Medical wards

Study pattern: Observational Study

Place of Study: C Ward. Christian Medical College, Vellore

Name of the Principal Investigator: Dr. Audrin Lenin, PG Registrar, Department of General Medicine

Name of the Guide: Dr. JV Peter, Professor, Department of Medicine

Approximate Number of Subjects: 220

Information sheet

Introduction: You are invited to take part in this research study to study if your illness is in any way contributing to the development of blood clots in your lets or your lungs. It is

not clear if medical illness, such as what you have, may increase your risk of developing blood clots and this study will look at this aspect.

Purpose of the research: A "thrombus" is a clot in the blood vessel which usually occurs due to three factors – alterations in flow of blood, increased tendency of the blood to clot, and injury to the blood vessel wall. Deep venous thrombus refers to a clot in the deep veins of the body. It is of concern because it can break off and lead to pulmonary embolism (clot in the pulmonary vessels) and in turn death if not identified and treated. Deep venous thrombosis is a common problem in hospitalized patients, especially in patients of intensive care. Numerous studies pointing towards the occurrence of deep venous thrombosis in medical wards despite measures to prevent the same, and limited studies on deep venous thrombosis in an Indian demographic, led us thinking on the lines of this topic, which necessitated a detailed evaluation and therefore shaping into this research paper.

Participant selection: You are being requested to participate/allow your relative to participate in this study as you/he/she have/has been admitted in *C Ward under Medicine Unit 2. The expected duration of the requested participation in this study would be 7 days from the time of admission into the ward, i.e., from the time of entering the study. In case you are discharged prior to that, we would only collect the information till the day you are admitted in hospital.

Voluntary participation: Your participation in this research is entirely voluntary. It is your choice whether to participate or not. Whether you choose to participate or not, the management and standard of care will remain the same. If you choose not to participate in this research project, you will still continue to receive the same standards of treatment. You may change your mind later and stop participating even if you agreed earlier. This will in no way affect the care that we provide to you.

Information on the research-Procedures & Protocol: We will perform scans (ultrasound scans) on the legs on Days 1, 3 and 7 to look for the presence of clots. Apart from this we will collect some information on the disease that you suffer from, details of treatment as well as test results to correlate. The scan itself is painless and does not cause any side-effects.

Appropriate Alternate Procedures: Other tests are available for detecting blood clots are more complex scans and tests like venogram (where a dye is injected into the leg and X-rays are taken to assess for clots). However although they may give more information they are more painful and can pose a small risk of developing allergy to the dye that is injected. If you need this test for further evaluation, we will talk to you about it.

Risks: There is a very minimal risk of dislodgement of a clot while doing the Doppler ultrasonography.

Benefits: The potential benefit is that these scans are not routinely done in patients admitted to the medical wards. If we do find a clot in the leg, we will inform your treating

doctors regarding it.

Reimbursements: You will not be charged for the cost of scan. There are no other incentives. You will not be paid for your participation in the study.

Confidentiality: We will ensure confidentiality of your name and no information that identifies you will be present once we analyze the information and send it for publication.

Sharing of the result: The result of this research is a property of Christian Medical College, Vellore; and I am entitled to publish it in a journal or present it in a conference. The participant will have no claim towards the same.

Right to Refuse or Withdraw: You do not have to take part in this research if you do not wish to do so. You may also withdraw participating in the research after giving the consent. It is your choice and all of your rights will be respected.

This proposal has been reviewed and approved by the research and ethics committee of the hospital whose task it is to make sure that research participants are protected from harm. If you wish to find about more about the IRB, contact

Research Office,

second floor,

Carman block,

Christian Medical College,

Bagayam, Vellore 632002.

Email:research@cmcvellore.ac.in

telephone: 04162284294.

It has also been reviewed by the Ethics Review Committee CMC Vellore, which is supporting the study.

If there are any further queries regarding this study or regarding the rights of the participants, you can contact me at

Dr. Audrin Lenin

PG Registrar,

Department of General Medicine,

Christian Medical College, Vellore.

Ph.No.: 9715916451

* Ward – C ward under Medicine Unit 2

** DVT – Deep Venous Thrombosis

@ Me/I – Principal Investigator

You – Subject/Participant

Date:

II.Certificate of Consent

Study Title: Determination of Incidence and Risk Factors of Deep Venous Thrombosis in a Medical Ward

Subject's Name: _____

Date of Birth / Age:_____

Please tick the boxes:

(i) I confirm that I have read and understood the information sheet dated _____ for the above study and have had the opportunity to ask questions. [ ]

(ii) I understand that my participation in the study is voluntary and that I am

free to withdraw at any time, without giving any reason, without my medical care or legal rights being affected. [ ]

(iii) I understand that the Sponsor of the clinical trial, others working on the Sponsor's behalf, the Ethics Committee and the regulatory authorities will not need my permission to look at my health records both in respect of the current study and any further research that may be conducted in relation to it, even if I withdraw from the trial. I agree to this access. However, I understand that my identity will not be revealed in any information released to third parties or published. [ ]

(iv) I agree not to restrict the use of any data or results that arise from this study provided such a use is only for scientific purpose(s) [ ]

(v) I agree to take part in the above study. [ ]

Signature (or Thumb impression) of the Subject/Legally Acceptable Representative:_____

Date: _____/_____/_____

Signatory's Name: _____

Signature of the Investigator: _____

Date: _____/_____/_____

Study Investigator's Name: _____

Signature of the Witness: _____

Date:_____/_____/_____

Name of the Witness: _____

ANNEXURE -3 IRB Protocol

APPLICATION FOR IRB APPROVAL OF OBSERVATIONAL (CASE-CONTROL / COHORT/ CROSS-SECTIONAL) STUDIES

CHRISTIAN MEDICAL COLLEGE, VELLORE

(Please complete Sections **I to III** and submit with all supporting documents)

SECTION I

Fluid Research Funding/External Funding

If for external funding, please provide name of funding agency and the application for submission in the funding agency's format, in addition to this application.

1. **Title of Research:** Incidence and risk factors of deep venous thrombosis among patients admitted to a medical ward at a tertiary hospital in South India.

2. **Title of Study (for lay public) :** Deep Venous Thrombosis in a medical ward

3. **Acronym if any : DVUS-M**

4. **Unique Protocol ID, if any**

5. **Name of the Principal Investigator:**

Audrin Lenin

Department of Medicine

Christian Medical College, Vellore

Vellore, Tamil Nadu

632004

If Post Graduate Registrar / Fellowship: Post graduate registrar

Enrollment date of PG Course: 06/2013

Completion date of PG Course: 05/2016

6. **Name of Guide (for Post-Graduate Registrar / Fellowship):**

Dr. John Victor Peter

Professor

Department of Critical Care

Christian Medical College, Vellore

7. Name and Designation of Co-Investigator(s), Employment Number and Address

Dr. Thambu David

Professor and Head

Medicine Unit 2

Christian Medical College, Vellore

Dr. Sudha Jasmine

Associate Professor

Medicine Unit 2

Christian Medical College, Vellore

Dr. Ravikar Ralph

Assistant professor

Department of Medicine

Christian Medical College, Vellore

Dr. Nathaniel Samson Devakiruba

Assistant professor

Department of Medicine

Christian Medical College, Vellore

Dr. Pavithra Mannam

Assistant Professor

Department of Radiology

Christian Medical College, Vellore

8. Department of Institution where the research will be carried out

Christian Medical College, Vellore

9. Names and addresses of other institutions where research will be carried out

-nil-

10. Duration of the Scheme.

2 years

11. Source/s of Monetary or Material Support

Internal Fluid Research Grant	: **Rs. 1,00,000**
External	: nil
Departmental fund	: **Rs. 2,500**

12.Objectives and aims of study

AIM

To assess the incidence of deep venous thrombosis and the risk factors favouring its development in patients admitted to a medical ward

OBJECTIVES

1) To assess the incidence of development of deep venous thrombosis among patients admitted in a medical ward at a tertiary care center in South India.
2) To evaluate the factors predisposing to the development of venous thrombosis in patients admitted in a medical ward.

13.Summary of the proposed research scheme (250 words).

Venous thrombosis and embolism is a common problem encountered in the medical wards (1) and is associated with significant contribution to health care cost. In 2010, the estimated heath care cost because of hospital acquired venous thromboembolism in the United States ranged from 6.8 to 36 billion dollars (2). There is a dearth of research involving venous thromboembolism in patients in medical wards in India.

This study would look at the incidence of a deep venous thrombosis in a medical ward in a tertiary hospital in South India. It would be a physician performed Doppler venous ultrasonography. This study would look at the risk factors of developing deep venous thrombosis and the outcomes.

The study will include all patients admitted to a medical ward during the study period. Patients admitted with a diagnosis of venous thrombosis or pulmonary embolism will be excluded. Patients on anticoagulation at the time of admission will also be excluded. An informed consent will be taken from all patients included in the study. A day 1 clinical research form will be filled. This would include demographics as well as known risk factors for the development of venous thrombosis. It has been shown that a single repeat study that is negative after 7 days predicts a less than 1% incidence of venous thrombus (3). Hence the Doppler ultrasonography will be performed on 1^{st}, 3^{rd} and the 7^{th} day of hospital admission for included patients. The investigator and co-investigators will undergo validation of their skills by the department of Radiology prior to the study. The Doppler sonography will be done over the popliteal and femoral vessels over the lower limbs and the juglar and axillary regions of the upper limb. A lack of compressibility or a visualization of the thrombus will be considered as positive for

venous thromboembolism (4). On day 7 or the day of discharge (whichever is earlier, the clinical research form will be completed with regard to the course and complications in the hospital. In the event of the presence of a deep venous thrombosis, the treating team shall be notified.

14.Present Knowledge and relevant bibliography

Deep vein thrombosis is the formation of clots in the peripheral veins of the body. It is common condition seen in hospitalized patients. The annual incidence of deep venous thrombosis is estimated at 1-3 per 1000 adult population.(2) In United States health care costs for total deep-vein thrombosis (DVT), total hospital-acquired DVT, and total "preventable" DVT. Annual cost ranges were obtained in 2010 US dollars for total ($7.5 to $39.5 billion), hospital-acquired ($5 to $26.5 billion), and preventable ($2.5 to $19.5 billion) DVT costs. When the sensitivity analysis was applied--taking into consideration higher incidence rates and costs - annual US total, hospital-acquired, and "preventable" DVT costs ranged from $9.8 to $52 billion, $6.8 to $36 billion, and $3.4 to $27 billion, respectively. (2) Among patients admitted in a Medical Ward, the incidence of deep vein thrombosis is 14.9%(1) In an Indian setup, the incidence of DVT was found to be 2.7 per 1000 person-days of hospital admission.

The major risk factors for development of venous thromboembolism are (1,5)

1) Age more than 75 years

2) Malignancy
3) Post-operative patients
4) Previous venous thromboembolism
5) Chronic respiratory disease
6) Heart disease
7) Obesity
8) Bed rest
9) NYHA class 3 and 4 heart disease
10) Sepsis
11) Stroke with lower limb weakness

The gold standard for diagnosis of a deep venous thrombosis is a contrast venogram. But it is not recommended as an initial screening test, as it a invasive procedure and obtaining an adequate study is difficult (5) Impedence plethysmography is another investigational modality used for diagnosis of a deep vein thrombosis. It's usage is limited by the fact that many facilities have neither the equipment nor skilled personnel to perform impedance plethysmography. It is the diagnostic modatily of choice in patients with recurrent deep vein thrombosis (5).

The most commonly used investigation for the diagnosis of a deep vein thrombosis is a doppler ultrasound. On an ultrasound the features suggestive of a deep vein thrombosis are –

- Abnormal compressibility of the vein
- Abnormal Doppler color flow
- The presence of an echogenic band
- Abnormal change in diameter during the Valsalva maneuver

It has been shown that the lack of compressibility of a vein alone with the ultrasound probe is highly sensitive (>95 percent) and specific (>95 percent) for proximal vein thrombosis (6–8) The limitation of a compression ultrasound are –

- It does not detect isolated thrombi in the iliac vein or that portion of the femoral vein within the adductor canal
- The results are limited in patients with deformities or a plaster cast.
- Serial studies need to be performed when the initial test is negative
    - Approximately 2 percent of patients with an initially negative ultrasound develop a positive study when retested seven days later
    - A single repeat study that is negative five to seven days after an initial negative study predicts a less than 1 percent likelihood of venous thromboembolism over months of follow-up
- Patients with pelvic neoplasms or abscesses may demonstrate isolated noncompressibility of the femoral vein when thrombosis is absent

Deep vein screening done at presentation and at day 7 were shown to have maximal accuracy in diagnosing deep venous thrombosis (6,9) It has been shown that a two point compression ultrasound done by emergency physicians after a 10 minute raining is as

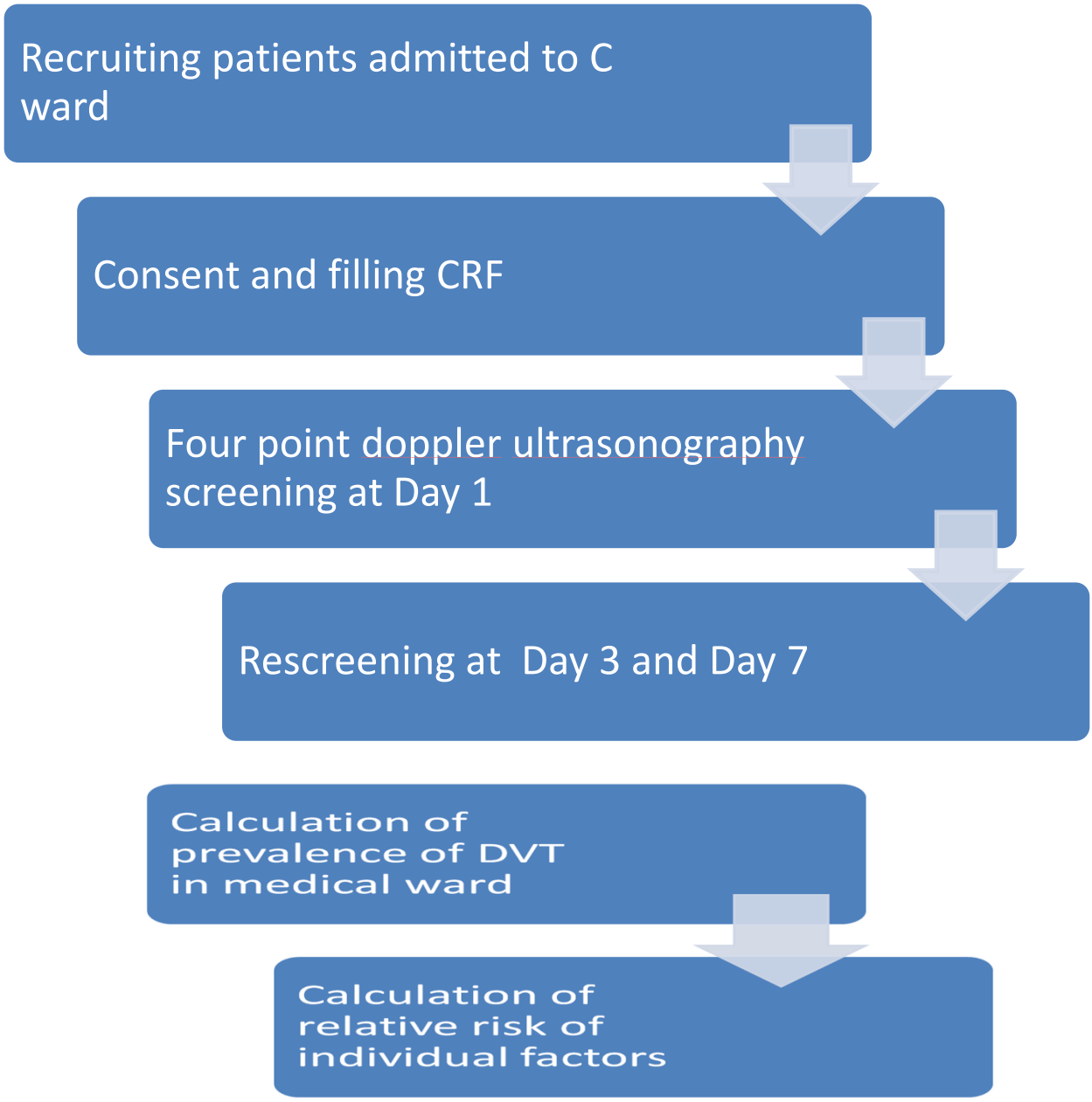
sensitive and aspecific to pick up a deep venous thrombosis as compared to a screening done by a radiologist (10)

In view of the current knowledge and a dearth of data from India, it would be relevant to look at the incidence of deep venous thrombosis in the Medical Ward at our hospital.

15. Preliminary work already done by the investigator in this problem: NIL

16. List of publications of the investigator in the field: NIL

17. Detailed diagrammatic Algorithm of the study



18.Detailed research plan:

a. **Setting:** Will be done from January 2014 to April 2015 in patients admitted in a medical ward under Medicine unit 2 at Christian Medical College, Vellore, a tertiary care center in South India.

b. **Participants:**

Inclusion criteria:

- Age >18 years
- Admitted to the Medical Ward under Medicine unit 2

Exclusion Criteria:

- Refusal to give consent
- Patients admitted with a diagnosis of DVT or pulmonary embolism
- Patients on therapeutic anticoagulation

c. **Variables:**

Oucomes:

DVT: Non-compressibility using a four point Doppler ultrasound at Day 1, Day 3 and Day 7 of hospital admission.

Death: Death of the subject within 7 days of hospital admission

Discharge: Discharge from the hospital within 7 days of hospital admission.

Exposures:

- Age
- Sex
- BMI
- Previous history of venous thromboembolism
- Whether on any anticoagulation
- Malignancy
- Stroke
- History of trauma
- History of surgery

- Central venous catheters - duration
- Dialysis ports
- Acute respiratory distress
- Congestive cardiac failure
- Hypercoagulable states
- Hormone therapy
- COPD
- Varicose veins
- Mobility

d. **Data Sources/measurement:**
Data will be collected on Day 1 of hospital admission through a clinical research form. Variables relating to treatment and outcome will be filled on Day 7 of hospital admission. The presence or absence of venous thromboembolism will be determined by Doppler ultrasonography on Day 1, Day 3 and Day 7 of hospitalisation. Recruitment of patients would be prospective and consecutive.

The data would be calculated as the incidence of development of DVT in terms of per 1000 patient days.

Prior to the commencement of the study, the skills of the principal investigator will be validated against a radiologist. The study will commence only after the validation is complete.

e. **Bias:** Describe
Logistical regression analysis will be done to negate the effect of confounders.

f. **Sample size**

$[\{Z(1\text{-alpha})\}^2 xPxQ]/ [D^2]$

Assuming incidence to be 14.9% (Mednox study), CI of 95% and error of margin of 5%

1. 195.92

Assuming an incidence of 15% drop out/loss of data, a sample size of 220 shall be considered.

19. Complete budget plan

*For **FLUID research grant money cannot be allocated for travel of the investigators nor can job outsourcing** be covered with FLUID grants. Funding out of the institution can be given only for the special mission hospital grant*

*(From Fluid Research Fund, there are no grants for personnel except in a major grant application, funding is limited **Rs. 40,000/- per year** for two years for standard applications, **Rs. 2,00,000/- per year for two years for major applications**). Website link: http://172.16.11.136/Research/#. > Rules for Major Fluid Research Grants. Do not exceed the budget allocated to you. In case the budget is exceeded, the amount will have to be deducted from one of your departmental special funds. Stationary, printing material and paper should not exceed more than 20% of the allocated fluid grant.*

*Please mention below the **breakdown of budget requested:** (The budgets that are drawn up should be comprehensive and should mention all subject in detail (For example – laboratory investigation should mention the specific category without generalization.)*

Timeline: 2yrs – Jan 2014 – Jan 2016

	Cost	Quantity	Total
Ultrasound package (D1/	Rs. 500	220	1,20,000
Miscellaneous	Rs. 2500	-	2500
Total			1,22,500

Requesting Rs. 1,00,000/- from FLUID research grant and Rs. 12,500/- from Departmental funds.

20. If this is an application for Fluid Research Funding, please provide name and account number of any other Fluid Research grant held by the PI.

-nil-

21. Informed Consent Documents (patient information sheet, investigator's brochure, drug information etc and informed consent document) please submit all translations with the proposal**.**

22. Inter-departmental cooperation:

i) Department of Radiology

The Department of Radiology is involved in the initial validation of this study as the primary diagnostic tool for case detection is an imaging modality, namely the ultrasound. 40 initial cases will enter this validation study and will be simultaneously screened by the principal investigator (self) and the radiologist. The sensitivity and specificity of the investigator's case

detection skills will be drawn against the radiologist, whose findings will be considered as the truth and the kappa value will be calculated.

ii) Department of Biostatistics

23. Signature of Principal Investigator

24. Signature of Guide/Head of the Department/ Unit

25. Co-Investigators' Consent (all co-investigators have to sign this form or supply separate letters of consent)

I/We give my/our consent to be a Co-Investigator and provide my/our expertise to the project. I/We have approved this version of the protocol and have contributed substantially to its development.

Name	**Department**	**Signature**	**Date**

Section II

APPLICATION FOR APPROVAL FROM ETHICS COMMITTEE OF THE

INSTITUTIONAL REVIEW BOARD OF CMC VELLORE FOR

ALL OBSERVATIONAL (CASE CONTROL, COHORT & OBSERVATIONAL) STUDIES IN HUMAN SUBJECTS

APPLICATION FOR ETHICS APPROVAL FOR ALL INTERVENTIONAL STUDIES IN HUMAN PARTICIPANTS

1. **Please provide a brief summary of the justification, objectives and methods in lay language, avoiding technical terms:**

   Formation of a clot in the blood vessels is known as a thrombus. The presence of the thrombus in the deep veins of the limbs is termed as a deep venous thrombosis. Deep venous thrombosis is a commonly encountered problem in hospitalized patients. The major dreaded consequence from deep venous thrombosis is pulmonary embolism (clot in the blood vessels of the lungs. Pulmonary embolism is the most common preventable cause of death among hospitalized patients in the United States. Several studies done in the west, have established the increased prevalence and incidence of deep venous thrombosis in patients admitted to medical wards, which have now paved way to an increase in the rate of awareness and implementation of prophylaxis.

   The limited number of studies done on the distribution of deep venous thrombosis among medical patients, especially in India led to this study being designed to determine the frequency of distribution of deep venous thrombosis in a protocolized environment like the medical intensive care unit, where patients are already on thromboprophylaxis; and to study the risk factors unique to the development of deep venous thrombosis among critically ill medical patients, despite

the prophylaxis. We hope that this study would bring to notice the interplay of several factors unique to hospitalized critically ill Indian medical patients, in the pathogenesis of deep venous thrombosis, which may inturn bring about several changes in our approach to the diagnosis, prophylaxis and treatment of the same; which would inturn benefit the community in the future.

This study will include all patients being admitted to a Medical Ward of Christian Medical College, Vellore. Informed consent will be obtained from all the participants of the study. Each participant will be followed up for a period of one week from the day of admission into the intensive care unit, during which information will be collected on the relevant present and past history, treatment details and outcome at the end of the study. In addition, each will receive three sequential ultrasound scans by the principal investigator (self) on day 1, 3 and 7 to screen for the presence of deep venous thrombosis in the upper and lower limbs.

2. **Please describe if the study uses procedures already being performed on patients for diagnosis or treatment or if modified or novel procedures are to be used?**

In this study the diagnostic modality used will be a compression ultrasound. Several studies have proved that the compression ultrasound used by criticare and emergency physicians is as good as the conventional duplex ultrasound done by the radiologists for the detection of deep venous thrombosis. The former is also a simpler technique which can be easily mastered by many, and also saves a lot of time and cost, compared to the latter.

Ultrasound scanning will be done on day 1, 3, and 7 from the time of admission into ICU on every participant. Each time, four points (2 in the upper extremity and 2 in the lower extremity) will be screened on both sides to look for evidence of deep venous thrombosis.

3. **Please describe what benefits might be reasonably be expected by the participant as an outcome of participation:**

The ultrasound testing for deep venous thrombosis is not routinely done on all patients in the medical ward and is done only in those with a high degree of clinical suspicion of deep venous thrombosis. This study will benefit every participant by offering them better than routine standards of care in the form of sequential ultrasound screening during the initial period of the ward stay, when studies have reported an increased occurrence of deep venous thrombosis. This study will therefore, help in early detection of deep venous thrombosis and therefore treatment of the same and prevention of its sequel in the patients.

4. **Please describe what benefits to others or new knowledge might be expected as a result of this study:**
   This study is aimed at studying the occurrence and factors playing a role in the development of deep venous thrombosis in the medical patients in India, especially in a South Indian demographic, wherein no other study has been previously attempted. This study is likely to pick up the risk factors unique to the population under study and thereby bring about a change in our approach to diagnosis, existing protocol for prophylaxis and treatment of the same, resulting in guidelines more appropriate to the targeted group.

5. **Who are to be enrolled?**
   All patients admitted in C Ward, Christian Medical College, Vellore, will be included in the study. Patients who have been admitted with a pre-existing diagnosis of deep venous thrombosis, those already on therapeutic anticoagulation, and those who refuse to be a part of the study will be excluded from the study group.

6. **If any vulnerable groups (e.g., pregnant women, children, economically disadvantaged individuals, etc) are to be enrolled, please provide a justification for their inclusion:**
   Nil

7. **What are the potential risks to participants in this study?**
   This study is not associated with any risks to the participant

8. **Are the risks to participants reasonable in relation to the benefits that might reasonably be expected as an outcome to the participant or to others, or the importance of the knowledge that may reasonably be expected to result? Please provide a detailed description of the above.**

   This study aims to describe the occurrence of deep venous thrombosis and study the risk factors in medical patients in an Indian demographic. The study is designed in such a way that no possible risks may be arise out of it. This study, by providing frequent sequential ultrasound imaging for detection of deep venous thrombosis, attempts to elevate the standards of care offered to the patients, by paving way for early detection and therefore treatment of deep venous thrombosis. As most of the protocols in place for diagnosis and prophylaxis of deep venous thrombosis are adapted from studies done on western population, this study hopes to determine the occurrence and the predictors for development of deep venous thrombosis, which would be helpful in determining the need for and creation of a protocol endogenous to the Indian hospitalized critically ill population.

9. **Regarding informed consent to obtained from research participants or their legally authorized representative(s):**

   a. **Does the informed consent document include all the required elements?**
      Yes(please find the informed consent form enclosed)

   b. **Are the participant information sheet and the consent document in language understandable to participants? (PLEASE PROVIDE WITH THIS SUBMISSION TRANSLATIONS IN ALL LOCAL LANGUAGES ANTICIPATED TO BE USED).**

      Yes (Please find copies of the informed consent enclosed)

   c. **Who will obtain informed consent (PI, nurse, other?) and in what setting?**

Principle investigator will obtain the informed consent in C ward

d. **If appropriate, is there a children's assent? If yes, please submit a copy of this form.**
No

e. **Is the EC requested to waive or alter any informed consent requirement?**
No

10. Is there provision of free treatment for research related injury? If yes, who will provide it?
Not applicable

11. Is there provision for compensation of participants for disability or death resulting from research related injury. If yes, who will provide it?
Not applicable

12. Is the study covered by insurance? If yes, please provide insurance documents from an Indian insurance company.
No

13. In addition to the overall budget in Section I, please provide details of the following

i) Justification, timing and amount of payments to study participants
ii) Justification, timing and amount of payments to investigators/departments
iii) Any other study related financial or in kind incentives to participants or study staff

Nil

14. Please describe the plan for maintaining confidentiality of study participant information.

All details for this study will be collected through a data abstraction form by the principal investigator**.**

15. **Please describe the plans for monitoring the safety of participants, reporting and managing adverse events. If this is an externally funded study with a Data Safety Monitoring Board, please provide the name and contact information of the DSMB chairperson.**
    Not applicable

16. **If applicable; please provide all significant previous decisions (e.g., those leading to a negative decision or modified protocol) by other ECs or regulatory authorities for the proposed study (whether in the same location or elsewhere) and an indication of the modification(s) to the protocol.**
    Not applicable

17. **If appropriate, has permission from the Drug Controller General of India been obtained?**
    Not applicable

18. **If this is international collaborative research, has permission from the Health Minstry's Screening Committee been obtained?**
    Not applicable

19. **For exchange of biological material in international collaborative studies, please provide a MoU/ Material Transfer Agreement between the collaborating partners.**

    Not applicable

20.Declaration (to be signed by all investigators)

By signing this form we give our consent to provide our expertise to the project. In addition:

a. We confirm that all investigators have approved this version of the protocol and have contributed substantially to its development.
b. We confirm that all potential authors are included in this protocol.
c. We confirm that we shall submit any protocol amendments, significant deviations from protocols, progress reports (if required) and a final report and also participate in any audit of this study, if required.
d. We confirm that we shall conduct this study in accordance with the Declaration of Helsinki; the ICMR Guidelines for Biomedical Research in Human Subjects 2006, with any subsequent amendments; and all applicable laws of the land.
e. We also agree to submit for publication to a peer reviewed journal the complete results of this study within two years of completion of this study.
f. We declare that we have no conflicts of interest that may affect the conduct or reporting of this study (OR) we declare the following conflicts of interest below.
g. We are aware of the institution's policies regarding scientific misconduct (Falsification/fabrication/plagiarism) and agree to abide by them.

2. Signature of Principal Investigator

3. Signature of Guide/Head of the Department/ Unit

Annexure 4 – Definitions

Well's score

- Clinically suspected DVT — 3.0 points
- Alternative diagnosis is less likely than PE — 3.0 points
- Tachycardia (heart rate > 100) — 1.5 points
- Immobilization (≥ 3d)/surgery in previous four weeks — 1.5 points
- History of DVT or PE — 1.5 points
- Hemoptysis — 1.0 points
- Malignancy (with treatment within 6 months) or palliative — 1.0 points

srnumb	name	hnum	age	sex	state	place	malig	surg	dvt	pe	smok	bed	cvs	vein	heart	htype	nyha	day1	day3	day7	day10	day14	day21	day30	DVT	chnite	chloc	diag	cvl	thbl	mobl	hcog	copt	dial	ards	chtp	prpt	plme	dura	consent	consently	Well's score	
4	Anuradha	8157466	29	2	Tamil Nad	Tiruvanna	2	2	2	2	2	2	2	2	2			1	1	99	99	99	99	99	1	99		Vaginal ca	2	2	2	1	Pregnancy	2	2	2		2	5	Yes	Phone	0	
9	Bharani	9151665	60	2	Andhra Pr	Chittoor	2	2	2	2	2	1	2	2	1	IHD	2	1	1	1	1	1	1	1	1	99		Left renal	2	2	2	2		2	2	2		2	16	Yes	Phone	1	
12	Bastian Az	8152168	61	1	Andhra Pr	Kadappa	2	2	2	2	2	1	1	2	1	IHD	2	1	1	1	1	1	99	99	1	99		CVA - Rigt	2	2	2	1	2	2	2	1	2	2	15	Yes	Phone	1.5	
15	Mothu Ser	8989758	37	2	Assam	Tinsuki Dis	2	2	2	2	2	1	2	2	2			1	1	99	99	99	99	99	1	99		Pancytopa	2	2	2	2		2	2	2		2	4	Yes	Phone	1.5	
19	Abhakumr	9153680	27	2	Jharkhand	Adityapur	2	2	2	2	2	1	2	2	2			2	2	2	2	2	2	2	2	2	Left axilla	Cryptococ	1	2	1	2		2	2	1	2	2	39	Yes	Phone	0	
28	Bidhun Lo	8981899	17	1	Jharkhand	Dumka	1	2	2	2	2	2	2	2	2	IHD	4	1	1	99	99	99	99	99	1	99		Right hilar	2	2	3	1	Malignanc	2	2	2		2	4	Yes	Phone	1	
28	Keseva D	9140859	65	1	Andhra Pr	Chittoor	2	2	2	2	1	1	2	2	2			1	1	1	99	99	99	99	1	99		Left lower	2	2	2	2		2	2	2		2	10	Yes	Phone	0	
30	Kidnapper	9157599	37	1	Tamil Nad	Vellore	2	2	2	2	1	1	1	2	2			1	1	1	1	99	99	99	1	99		Young stro	2	2	1	1	Polycythe	2	2	2		2	10	Yes	Written	1.5	
35	Muneeraw	5070457	50	2	Andhra Pr	Chittoor	2	2	2	2	2	2	2	2	2			1	1	1	99	99	99	99	1	99		Bronchial	2	2	3	2		2	2	2		2	9	Yes	Phone	1.5	
37	Asha	9150737	21	2	Andhra Pr	Chittoor	2	2	2	2	2	2	2	2	2			1	1	1	1	1	1	99	1	99		OP Poisor	2	2	1	2		2	2	1		2	28	Yes	Phone	1.5	
38	Chengaiy	8285649	88	1	Andhra Pr	Chittoor	2	2	2	2	1	1	2	2	2	IHD	3	1	1	99	99	99	99	99	1	99		COPD, Dbl	2	2	2	2		2	2	2		2	4	Yes	Phone	2	
40	Turaka Ch	9150656	55	2	Andhra Pr	Kadappa	2	2	2	2	2	1	2	2	2			1	1	1	1	1	99	99	1	99		THGN, Ca	1	2	1	2		2	1	1	2	2	15	Yes	Phone	3	
44	Mary Mall	8180976	57	2	Andhra Pr	Chittoor	2	2	2	2	2	1	2	2	2			1	1	99	99	99	99	99	1	99		UTI, Sepsi	2	2	2	2		2	2	2		2	6	Yes	Phone	1.5	
47	Sulochana	9663376	54	2	Tamil Nad	Vellore	2	1	2	2	2	2	2	2	2			1	99	99	99	99	99	99	1	99		Angioede	2	2	3	2		2	2	2		2	2	Yes	Written	1.5	
52	Kamineni	2335985	17	1	Andhra Pr	Kadappa	2	2	2	2	2	1	2	2	2			1	1	1	99	99	99	99	1	99		Reactive a	2	2	2	2		2	2	2		2	10	Yes	Phone	0	
56	Ganmuthi	9172809	56	2	Jharkhand	Saraikella	2	2	2	2	2	1	2	2	2			1	1	99	99	99	99	99	1	99		DIC, Septi	1	2	1	2		2	1	2		2	4	Yes	Phone	3	
57	Lakshmi	9173844	50	2	Tamil Nad	Tiruvanna	2	2	2	2	2	1	1	2	2			1	1	99	99	99	99	99	1	99		CVA - Rigt	2	2	2	1	2	2	2	1	2	2	3	Yes	Written	1.5	
68	Vijai Kum	9234869	27	1	Tamil Nad	Vellore	2	2	2	2	2	2	1	2	2			1	1	1	1	99	99	99	1	99		Meningoe	2	2	2	1	2	2	2	1	1	2	12	Yes	Written	1.5	
71	Venkatesl	2434454	21	1	Tamil Nad	Villupuran	2	2	2	2	2	2	2	2	2			1	1	99	99	99	99	99	1	99		Malaria	2	2	3	2		2	2	2		2	5	Yes	Written	1.5	
81	Sivalingan	8429426	82	1	Tamil Nad	Vellore	2	2	2	2	1	2	2	2	2			1	1	99	99	99	99	99	1	99		ATT induc	2	2	1	2		2	2	1	2	2	4	Yes	Written	1.5	
87	Jayachand	8416661	32	1	Tamil Nad	Vellore	2	2	2	2	2	2	2	2	2			1	99	99	99	99	99	99	1	99		Malaria, H	2	2	3	2		2	2	2		2	3	Yes	Written	0	
91	Mohideer	6112331	62	1	Tamil Nad	Vellore	2	1	2	2	1	1	2	2	2			1	2	2	2	2	2	99	2	2	R/femoral	Enterococ	2	2	1	2		2	2	1	2	2	25	Yes	Written	4	
99	Manimuju	9261805	60	1	Tamil Nad	Walajah	2	2	2	2	2	2	2	2	2			1	1	2	2	2	99	99	2	2	Right femi	Prostatic a	2	2	3	2		2	2	2		2	18	Yes	Written	4.5	
101	Sulaimal	6543348	89	2	Tamil Nad	Vellore	2	2	2	2	2	2	1	2	2			1	99	99	99	99	99	99	1	99		Parkinson	2	2	2	2		2	2	1	2	2	2	Yes	Written	1.5	
104	Dhanesh K	9282809	51	2	Tamil Nad	Vellore	2	2	2	2	2	2	2	2	2			1	1	99	99	99	99	99	1	99		Dengue fe	2	2	3	2		2	2	2		2	4	Yes	Written	0	
108	Attaullah	8067886	44	1	Tamil Nad	Ramipet	2	2	2	2	1	2	2	2	2			1	1	99	99	99	99	99	1	99		BIH, HT, D	2	2	3	2		2	2	2		2	4	Yes	Written	3	
118	Saravanat	5267599	39	2	Tamil Nad	Arcot	2	2	2	2	2	2	2	2	2			1	1	99	99	99	99	99	1	99		Scrub Typl	2	2	3	2		2	2	2		2	4	Yes	Written	1.5	
121	Jagnatha	5264679	26	1	Tamil Nad	Vellore	2	2	2	2	2	2	2	2	2			1	1	99	99	99	99	99	1	99		Scrub Typl	2	2	3	2		2	2	2		2	5	Yes	Written	0	
130	Elumalai	9284447	60	1	Tamil Nad	Tiruvanna	1	2	2	2	2	2	2	2	2			1	1	1	99	99	99	99	1	99		Ca Navopl	2	2	3	2		2	2	2		2	9	Yes	Written	1	
133	Dasadhara	3263816	55	1	Tamil Nad	Vellore	2	2	2	2	2	2	2	2	2	IHD	2	1	1	1	1	99	99	99	1	99		Pyelonepl	2	2	3	2		2	2	1	2	2	13	Yes	Written	0	
152	Pangunan	9677216	63	1	Tamil Nad	Vellore	2	2	2	2	1	1	1	2	2	IHD	3	1	1	1	1	99	99	99	1	99	'	CVA - Pon	2	2	1	2		2	2	2		2	10	Yes	Written	1.5	
158	Mallga	9686187	54	2	Tamil Nad	Vellore	2	2	2	2	2	2	2	2	2			1	1	99	99	99	99	99	1	99		LRI, HT	2	2	3	2		2	2	2		2	6	Yes	Written	1.5	
160	Nagalaksh	7620731	70	2	Tamil Nad	Vellore	2	2	2	2	2	1	2	2	2	IHD	3	1	1	1	99	99	99	99	1	99		IHD, NSTE	2	2	2	2		2	2	1	2	2	10	Yes	Written	1.5	
175	Debika Da	4348251	52	2	Jharkhand	Midnapor	2	2	2	2	2	2	2	2	2			1	1	99	99	99	99	99	1	99		DSA, Obes	2	2	3	2		2	2	2		2	3	Yes	Phone	0	
183	Mamta De	8187725	44	2	Jharkhand	Dhanbad	2	2	2	2	2	1	1	2	2			1	1	99	99	99	99	99	1	99		TB Mening	2	2	1	2		2	2	1	2	2	5	Yes	Phone	4.5	
189	Pechiappa	2023208	40	1	Tamil Nad	Vellore	2	2	2	2	2	1	2	2	2			1	1	99	99	99	99	99	1	99		Pulmonar	2	2	3	2		2	2	2		2	5	Yes	Written	2.5	
190	Vikram Ch	1981439	29	1	Jharkhand	Deoghar	2	2	2	2	2	1	2	2	2			1	1	99	99	99	99	99	1	99		Pulmonar	2	2	3	2		2	2	2		2	6	Yes	Phone	0	
193	Geeta Dev	8187121	46	2	Bihar	Gaya	2	2	2	2	2	2	1	2	2			1	1	1	1	99	99	99	1	99		Diabetic n	2	2	2	2		2	2	2		2	14	Yes	Phone	4.5	
199	Ravikuma	8670911	52	1	Tamil Nad	Vellore	2	2	2	2	2	1	2	2	2			1	1	99	99	99	99	99	1	99		Ascites un	2	2	2	2		2	2	2		2	4	Yes	Written	2.5	
203	Sajitha Be	4022686	62	2	Tamil Nad	Vellore	2	2	2	2	2	1	2	2	2			1	1	99	99	99	99	99	1	99		Left tibia f	2	2	2	2		2	2	2		2	3	Yes	Written	2	
209	Krishnan	9525568	35	1	Tamil Nad	Vellore	2	2	2	2	2	1	2	2	2			1	1	1	99	99	99	99	1	99		Cerebral r	2	2	2	2		2	2	2		2	7	Yes	Written	1.5	
212	Murugesa	8196270	60	1	Tamil Nad	Vellore	2	2	2	2	2	2	2	2	2			1	1	99	99	99	99	99	1	99		DM, DL, PI	2	2	3	2		2	2	2		2	6	Yes	Written	0	
217	Sasikala	9527219	59	2	Tamil Nad	Vellore	2	2	2	2	2	2	2	2	2			1	1	1	99	99	99	99	1	99		Post aborti	2	2	3	2		2	2	2		2	8	Yes	Written	1.5	